

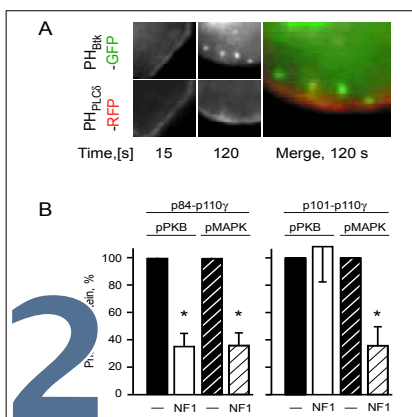


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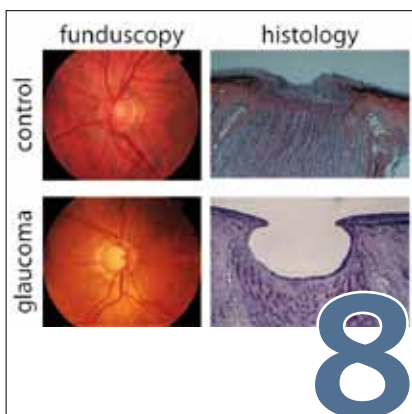
FACTS

Periodisches Informationsblatt des Departementes Biomedizin
Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

INHALT CONTENTS



Lipid Signaling in Physiology and Disease - from Molecular Mechanism to PI3K Targeting Strategies
 from Matthias Wymann



Understanding glaucoma: intricate networks and amazing architecture
 from Albert Neutzner



Zur Emeritierung von Uwe Otten



PhD Club



Ein Arbeitstag in der Shanti-Station in Kathmandu/Nepal

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IMPRESSUM

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EDITORIAL



Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Die erste Jahreshälfte liegt hinter uns. Am 15. Mai 2011 hat das Basler Stimmvolk dem Gesetz über die öffentlichen Spitäler des Kantons Basel-Stadt und damit der Verselbstständigung des Universitätsspitals Basel zugestimmt. Dieser Entscheid bietet gute Voraussetzungen, das USB im künftig intensiveren Wettbewerb der Spitäler erfolgreich zu positionieren.

Nach fast vierzig Jahren aktiver und erfolgreicher Tätigkeit in Lehre und Forschung am Departement Biomedizin und der Universität Basel hat Uwe Otten Ende April 2011 das DBM verlassen. Die Forschung von Uwe Otten wurde anlässlich eines internationalen Symposiums am 28. April 2011 (S. 29) gewürdigt. Auch von meiner Seite noch einmal ganz herzlichen Dank an Uwe Otten für seine vielen Beiträge und seinen ansteckenden Enthusiasmus!

In der Sommerausgabe der DBM Facts nimmt Matthias Wymann uns mit in die Welt der Signalübermittlung durch Lipide bei Entzündungsvorgängen und Krebs (S. 2), und von Albert Neutzner erfahren wir mehr über die Forschung zur Pathophysiologie der Entstehung von Glaucomerkrankungen (S. 8). Ein Schwerpunkt dieses Heftes ist die Entwicklungshilfe, die von Mitarbeitenden des DBM geleistet wird. So schildert Frances Kern ihren Aufenthalt in einer Leprastation in Kathmandu (S. 30) und Vivian Kiefer berichtet über ihre diversen Projekte im Rahmen ihrer Tätigkeit für den Verein Philippinischer Migrantinnen und Migranten «Maharlika Schweiz» (S. 37).

Spannende Lektüre, einen schönen Sommer, erholen Sie sich gut!

Dear Readers

The first half of the year is behind us. On the 15th May 2011 the voters of Basel voted in favour of the bill regarding the public hospitals in the canton of Basel and thus for the independence of the University Hospital of Basel. This decision will allow the USB to be favourably placed in the intensifying competition amongst the hospitals.

After nearly 40 years of active and successful employment teaching and researching at the Department of Biomedicine Uwe Otten left the DBM at the end of April 2011. The research of Uwe Otten was honoured by means of an International symposium on the 28th April 2011 (page 29). I would like to thank Uwe Otten again for his many contributions and his contagious enthusiasm!

In this summer edition of DBM Facts Matthias Wymann brings us into the world of lipid signal transduction in inflammatory processes and cancer (page 2), and Albert Neutzner teaches us more about the research into pathophysiology of the development of glaucoma (page 8). One main focus of this issue is on the foreign aid that is given by members of the DBM. Frances Kern describes her stay at a leper colony in Katmandu (page 30) and Vivian Kiefer tells us about her divers projects relating to her involvement with the Society for Filipino migrants "Maharlika Schweiz" (page 37).

Enjoy reading, have a lovely summer and relax well!

Lipid Signaling in Physiology and Disease – from Molecular Mechanism to PI3K Targeting Strategies



From top left: → Vladmimir Cmiljanovic (Chemist), Matthias Wymann, Jan Vözlmann, Ruben Cal (Chemist), Florent Beaufils (Chemist), → Romy Walser, Poppy Fotiadou, Mirjam Zimmermann, Elena Gogvadze, → Dominik Erhart, Serdar Korur, Fabrizio Botindari (missing on the picture are Thomas Bohnacker, Romina Marone, Anna Melone, Hannes Merz, Ann Mertz Biro).

To serve us well, all cells in our body have to fulfil their task in a concerted action. Normally, cells receive and release signals and integrate them properly. These signals are processed by cell surface or intra-cellular receptors coupled to a plethora of intracellular signal transduction cascades. In diseases like chronic inflammation, autoimmunity, cancer, but also cardiovascular disease – and even back pain, cellular signals overshoot and can cause morbidity and death. Many signal transduction pathways start at membranes (Wymann and Schneider, 2008), and it is here where the lipid kinase called phosphoinositide 3-kinase (PI3K) acts. PI3K controls cellular hemostasis and contributes to the over-activation of many cell types. In this respect, PI3Ks have been shown to be key in the control of cellular metabolism, growth, proliferation, survival and migration, intracellular membrane transport, secretion and more (see Fig. 1, (Wymann and Marone, 2005)).

Cancer and inflammatory disease include a wide variety of disorders with a broad degree of severity and clinical outcome. But in essence both emerge from pre-existing, but derailed physiologic repair and defense mechanisms. When a cell switches from a quiescent to an activated state to enter a tissue repair or host defense mode, this often involves the activation of PI3K.

Phosphoinositides – hemostasis and disease

Cell surface receptor-controlled PI3Ks are called class

I PI3Ks, and are the only ones to produce the lipid PtdIns(3,4,5)P₃. PtdIns(3,4,5)P₃ provides docking sites for signaling molecules with lipid receptor domains (Lemmon, 2008) at the inner leaflet of the plasma membrane, and the lipid is thus a nucleation point for many signaling cascades. One of the master kinases recruited by PtdIns(3,4,5)P₃ is the Ser/Thr protein kinase B (PKB, also called Akt). PKB indirectly activates the target of rapamycin (TOR or mammalian TOR, mTOR), which is an important hub sensing energy and nutrient supply to regulate protein synthesis and growth.

Crucial findings of the PI3K/PKB/TOR pathway have been contributed by groups that are present in Basel: the identification of the first PI3K inhibitor wortmannin (Arcaro and Wymann, 1993) made PI3K studies possible to everybody, the cloning of PKB (called “Rac kinase” at that time; (Jones et al., 1991) provided the first downstream target for PI3K, and the discovery of the TOR complex (Kunz et al., 1993) initiated the elucidation of nutrient sensing and growth control. In the last two decades, the PI3K/PKB/TOR field came a long way: while the signaling map was essentially blank in the early nineties, a dense and complex network of signaling components was uncovered in the mean time. The achievements of the field will be celebrated with a dedicated conference (TOR, PI3K and Akt – 20 years on; see <http://www.torandmore.org>) here in Basel in September. PtdIns(3,4,5)P₃ does not only recruit PKB, but also trig-

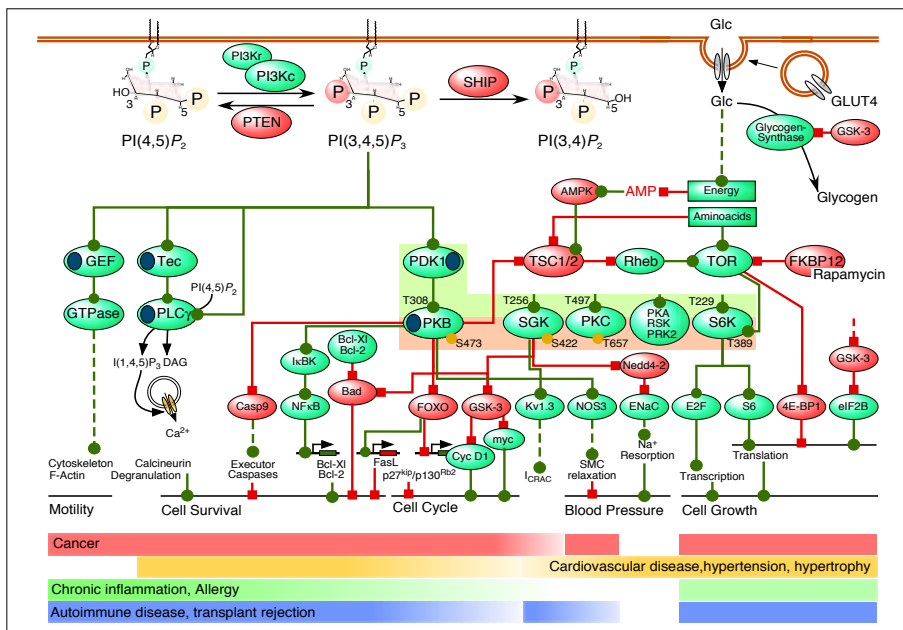


Fig. 1. Coupling of PI3K signaling to physiologic processes and disease. Upon cell surface receptor stimulation, class I PI3K heterodimers produce PtdIns(3,4,5)P₃ at the plasma membrane to provide docking sites for pleckstrin homology domain containing proteins like protein kinase B (PKB). The processes listed at the bottom of the scheme were connected to the displayed signaling pathways using genetic and pharmacological evidence. For further details of the role of lipid signaling in disease see (Wymann and Marone, 2005; Wymann and Schneider, 2008).

gers the activation of guanine nucleotide exchange factors (GEFs), which subsequently increase Rho GTPase activity and initiate cytoskeletal rearrangements, cell polarity and migration. The importance of PtdIns(3,4,5) P_3 levels in disease has been validated by the loss of one of the counter-players of PI3Ks: when the lipid 3'-phosphatase PTEN (Phosphatase and Tensin homolog deleted on chromosome Ten) is lost, PtdIns(3,4,5) P_3 levels rise, and the lipid shows its oncogenic potential (Zhang and Yu, 2010). Most cases of Cowden Syndrome are due mutations in PTEN, and result in the formation of hyperplasia and adenoma, which constitute early forms of cancer. The lack of lipid phosphatases degrading PtdIns(3,5) P_2 or PtdIns-3- P causes progressive disease, for example mutations in the gene coding for myotubularin 1 (MTM1) cause X-linked myotubular myopathy (XLMTM), and loss of phosphatase activity in myotubularin-related protein 2 (Mtmr2) can cause Charcot-Marie-Tooth disease type 4B1 (CMT4B1, (Berger et al., 2002; Cao et al., 2008)). These aberrant changes illustrate how a delicate balance between lipid kinase and lipid phosphatase activities is required to maintain the flux through the phosphoinositide pathway, and that phosphoinositide levels play an important part in cellular homeostasis (Fig. 1).

Our research group has a long-standing interest in PI3K signaling in inflammation and cancer. To investigate these fields, we have, in the past, initiated several programs to study the role of various PI3K isoforms by genetic and pharmacological means. Latest efforts also include the production of chemical tools to elucidate spatial PI3K signaling. Recent results have demonstrated that PI3K produces functionally distinct pools in membrane micro-domains.

Spatial regulation of PI3K signaling – context dependent in- and output

PI3Ks are constituted of an adaptor and a catalytic subunit. We have recently established, that the adaptor subunit can selectively relay PI3K signaling to distinct cellular responses. Using bone marrow derived mast cells (BMMCs) derived from PI3K γ null mice, we could establish reconstitution assays combining the catalytic subunit of PI3K γ (called p110 γ) with one of the two

adaptor units p84 or p101. Interestingly, both adaptor units promoted chemotaxis in response to ligands of G protein-coupled receptors (GPCRs), but only the p84-p110 γ complex participated in mast cell degranulation responses. The reason for this remained a riddle, until it became clear that the p101-p110 γ complex produced PtdIns(3,4,5) P_3 at the plasma membrane that was rapidly internalized after GPCR stimulation (Fig. 2A; for details see (Bohnacker et al., 2009)). In brief, this work established for the first time the existence of distinct, functionally non-redundant pools of PtdIns(3,4,5) P_3 in the plasma membrane. These two lipid pools could

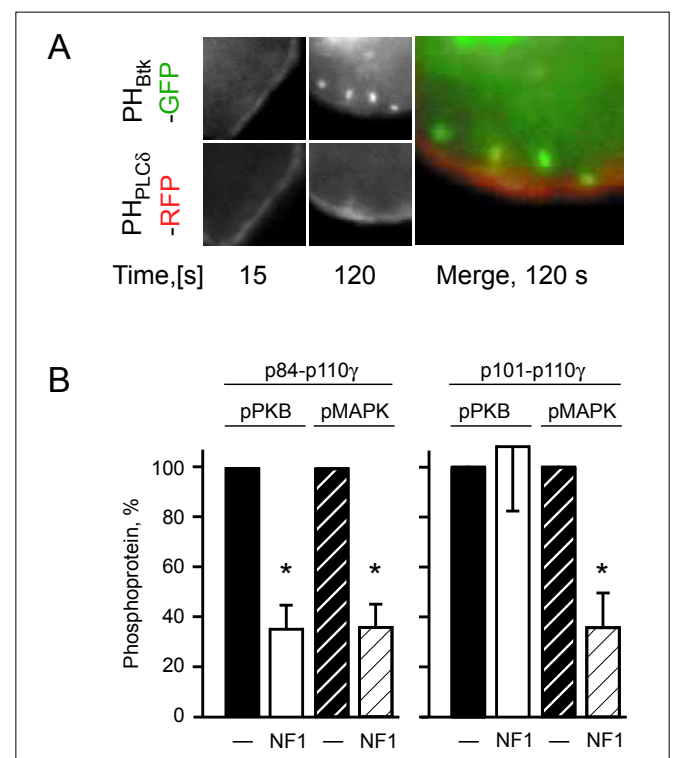


Fig. 2. Spatial signaling by PI3K in adenosine stimulated bone marrow-derived mast cells (BMMCs): PI3K γ is composed of an adaptor subunit (either p84 or p101) and a catalytic subunit p110 γ . **A)** When activated, the p101-p110 γ complex produced PtdIns(3,4,5) P_3 at the plasma membrane at early times, but PtdIns(3,4,5) P_3 was internalized >60 seconds after stimulation. PtdIns(3,4,5) P_3 is detected here with a pleckstrin homology from Bruton's tyrosine kinase fused to GFP (PH^{Btk}-GFP, green), while PtdIns(4,5) P_2 is depicted in red (PH^{PLC δ} -RFP). Interestingly, PtdIns(3,4,5) P_3 clearly segregates from PtdIns(4,5) P_2 , although the latter is present at a 100x higher concentration in the plasma membrane as compared to PtdIns(3,4,5) P_3 . **B)** The phosphorylation of the PI3K downstream target PKB/Akt is sensitive to co-expression of the RasGAP NF1 when initiated by p84-p110 γ , while p101-p110 γ complexes relay the GPCR signal in a Ras-independent fashion. The phosphorylation of the mitogen activated protein kinase (MAPK) was used as an indicator of the Ras status, as active Ras is required to induce the Raf/MEK/MAPK axis.

also be distinguished by their different sensitivity to cholesterol depletion. Furthermore, it could be established that the p84-p110 γ complex could only signal in the presence of activated, GTP-bound Ras, while p101-p110 γ complexes were resistant to Ras inactivation (e.g. by the action of the Ras GTPase activating protein NF1, Fig. 2B; (Kurig et al., 2009)). Moreover, it became clear that PI3K γ can be activated by the phosphorylation by protein kinase C β in mast cells. This process requires the influx of extracellular Ca²⁺ through store operated Ca²⁺ channels, and supports sustained mast cell activation in a late phase (Walser *et al.*, unpublished). In contrast to the activation by PKC β , protein kinase A (PKA) inactivates PI3K γ by a C-terminal phosphorylation (Perino et al., 2011). Ongoing work illustrates that PI3K γ is a heavily regulated enzyme, and that PI3K γ – which normally operates downstream of GPCRs – can be disconnected from GPCRs to relay Ca²⁺ signaling. The insight obtained in the regulation of PI3K γ signaling can be exploited to develop cell and tissue-specific targeting strategies for PI3K γ in allergy: presently explore possibilities to pharmacologically inactivate mast cells, without affecting the action of cells involved in host-defense reactions.

A Role for PI3K γ in obesity and thermogenesis

As mentioned above, PI3K γ plays a central role in the control of adhesion, migration, degranulation, and cardiac contractility. When mice without functional PI3K γ are fed a normal diet (chow diet), no changes in body weight or fat are apparent during their lifespan as compared to wild type animals. It was therefore a surprise that PI3K γ null mice remained lean on a high fat diet, while wild type counterparts increased fat mass, and developed a type II diabetes phenotype including insulin resistance and increased blood glucose levels (collaboration with G. Solinas, Fribourg). In parallel, PI3K γ null mice were also protected from a dramatic hepatic steatosis found in wild type animals on high fat diet. As cytokine levels and macrophages in adipose tissue were increased on high fat diet, we initially assumed that hematopoietic cells would play a major role in the development of obesity and insulin resistance, as we have observed previously that macrophage migration towards inflamed tissues is impaired in PI3K γ null mice (for a review see (Wyman et al., 2003)). Bone marrow

transplantations demonstrated, however, that the role of PI3K γ in obesity was mainly restricted to the host tissue, not the hematopoietic system (Fig. 3). Calorimetric measurements revealed that PI3K γ plays a role in the regulation of thermogenesis, and is increasingly expressed in white and brown fat of obese animals. Inactivation of PI3K γ thus renders mice obesity resistant by increasing adaptive heat dissipation and oxygen consumption, while calorie intake remains unaltered (Becattini *et al.*; PNAS, under revision). While the PI3K γ -dependent non-hematopoietic tissue could include adipocytes, the involved cell types and the exact underlying mechanism will have to be studied using tissue-specific knock-out mice. The above findings, together with previous results obtained in mouse models of atherosclerosis (Fougerat et al., 2008), hypertension (Vecchione et al., 2005), cardiac hypertrophy (Crackower et al., 2002; Patrucco et al., 2004) and thrombus forma-

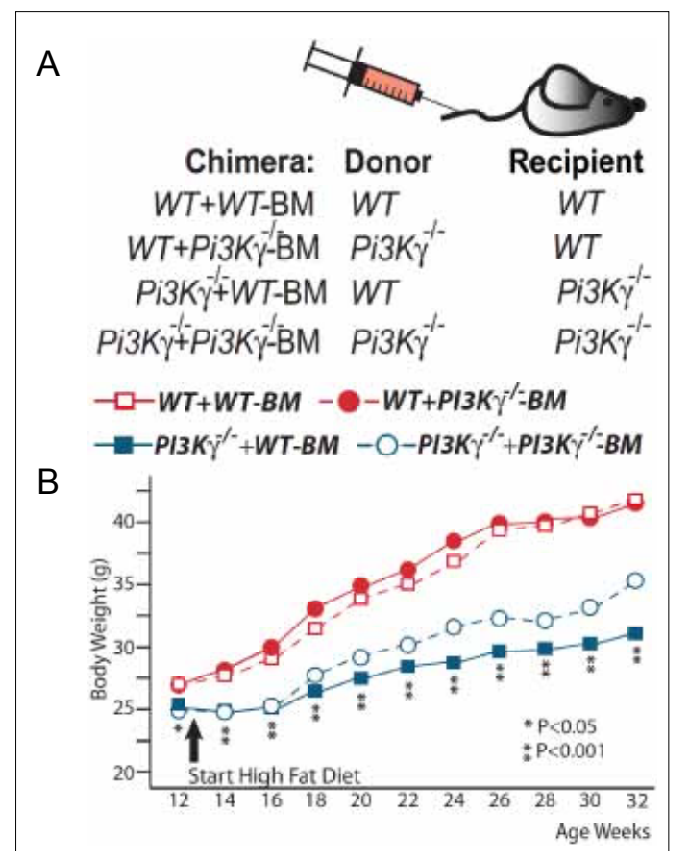


Fig. 3. Mouse chimeras were produced using wild type and PI3K γ null host animals and wild type and PI3K γ null bone marrow. The four resulting combinations are depicted in A). B) The gain of body weight was linked to the wild type host body, but independent of the presence of PI3K γ in the hematopoietic compartment (Becattini et al.; PNAS, under revision).

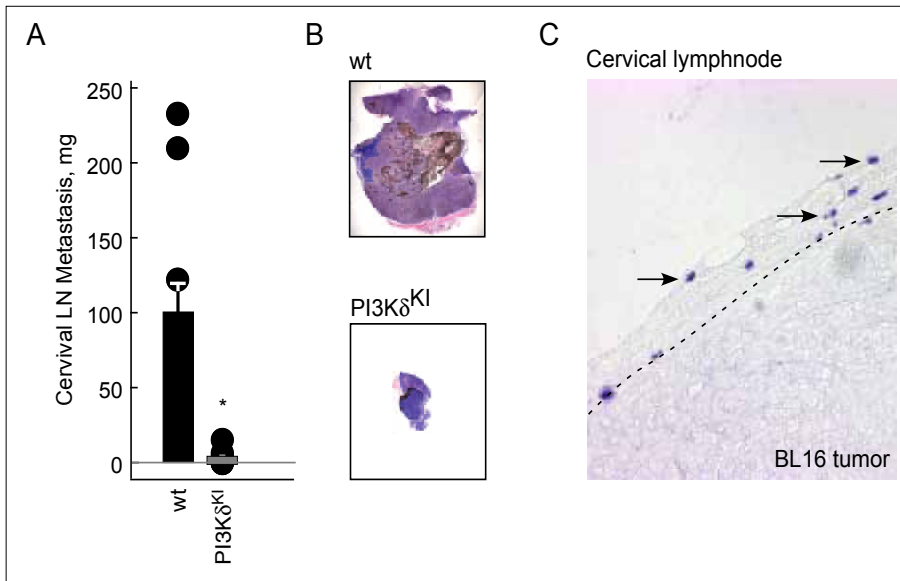


Fig. 4. Importance of PI3K signaling in host immune system and melanoma tumors. To evaluate the importance of PI3K signaling in the host immune system, BL16 melanoma cells were intradermally inoculated into the ear of genetically modified animals. Results obtained with wild type mice and mice expressing a catalytically inactive PI3K δ (knock-in mice, PI3K δ ^{KI}) are shown here. **A**, **B**) While wild type mice developed metastatic melanoma in cervical lymph nodes (LN), PI3K δ ^{KI} were largely protected against metastasis in lymph nodes. **C**) Metastatic tumors in wild type animals displayed high numbers of mast cells in the capsule of the lymph node (arrows point to mast cells). In PI3K δ ^{KI} animals, mast cells could not be detected in the lymph node of healthy and tumor bearing mice (Marone et al., unpublished).

tion (Hirsch et al., 2001), suggest that targeting of PI3K γ might be attractive in obesity-related insulin resistance and associated cardiovascular disease conditions.

Individual class I PI3K isoforms in cancer

Initially, class I PI3Ks were discovered to be associated with viral oncogenes, and for the last two decades the link between cancer and elevated PtdIns(3,4,5) P_3 levels has been corroborated. While activating mutations are frequently found in the catalytic subunit of PI3K α (called p110 α) in a wide variety of tumors, also the PI3K β isoform plays a role in cancer progression, including breast (Ciraolo et al., 2008) and prostate cancer. As a consequence, pan-PI3K inhibitors were successfully used to attenuate tumor progression ((Marone et al., 2009); for a review see (Marone et al., 2008)). While basically any activated class I PI3K can drive growth and proliferation, PI3K isoforms might also play distinct roles in the modulation of host anti-tumor responses and angiogenesis. A better understanding of the role of PI3Ks in pro- and anti-tumoral responses contributes therefore to strategies to refine PI3K inhibitor profiles to be used in oncology. The use of a syngeneic BL16 cell melanoma mouse model has helped to identify non-redundant actions of PI3K β , PI3K δ , and PI3K γ . The loss of function of PI3K δ in the host, for example, protected tumor mice completely from the formation of lymph node metastasis. Interestingly, this correlates with the absence of mast cells even from normal lymph nodes. While roles for macrophages

in tumor angiogenesis and tumor metastasis have been established, it is not clear how mast cells contribute to the colonization of lymph nodes by metastatic melanoma. The investigation of tissue-specific genetically targeted mice, *in vivo* cellular complementation studies, and immune-modulatory approaches are ongoing to unravel the cellular networks modulating melanoma dissemination.

As a whole, we aim to elucidate lipid signaling in inflammation and cancer, and to provide novel insights to devise strategies for novel therapies. To expand our possibilities, we have started some time ago to collaborate with chemists (E. Constable and B. Giese), to generate molecular tools to study signal transduction, and to modulate PI kinase activities. This work has already generated several joint patent applications, and has helped to initiate a network founded by the European Science Foundation (ESF) with the aim to develop further molecular probes to track phosphoinositide signaling in space and time.

Matthias Wymann

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Understanding glaucoma: intricate networks and amazing architecture

The main goal behind the research in the lab "Ocular Pharmacology and Physiology" is to understand the processes leading to glaucoma - a quite common neurodegenerative disorder. We follow two lines of investigation: we study the amazing architecture of meningotheelial cells and the environment they form around the optic nerve and we are also fascinated by the intricate networks formed by mitochondria and their connection to mitochondrial health and glaucomatous neurodegeneration.



Figure 1: The group "Ocular Pharmacology and Physiology". From left to right and back to front: Roy Allenspach, Charles Hemion, Albert Neutzner, Peter Meyer, Lei Fang, Anne-Sophie Benischke, Claudia Bippes, Monique Sauter. Missing from the picture is Tatjana Binggeli.

Glaucoma is a leading cause of blindness and affects over 60 million patients worldwide. Clinically, this condition presents with a diminished field of vision and ultimately loss of sight, resulting from the slowly progressing degeneration of retinal ganglion cells and their axons making up the optic nerve. One hallmark of glaucoma that distinguishes this disease from other optic nerve disorders is the remodelling of the optic nerve head or excavation of the optic disc (see Figure 2). Due to the slow progression of the disease and the astonishing capabilities of the visual cortex to fill in missing visual information (think: blind spot), patients oftentimes see a doctor only after the irreparable damage to the optic nerve has already occurred. Despite one century of intense research, the underlying cause for glaucomatous neurodegeneration is still debated. One major – and the most accepted – risk factor for glaucoma is elevated intraocular pressure. However, elevated pressure does not inevitably cause glaucoma and lowering it using medication is not necessarily enough to halt the progression of the disease. Interestingly, so called normal tension glaucoma, where intraocular pressure is not elevated but rather remains normal, occurs in around 20% Caucasians and in about 90% of patients in the Asian population. Therefore, additional causes or factors for glaucoma pathogenesis are likely at play. Consequently, impaired ocular perfusion caused by vascular dysregulation is discussed as a second risk factor for glaucoma development. The eye and especially retina and optic nerve are exquisitely oxygen-dependent tissues and therefore rely heavily on sufficient blood supply. Vasospasms as a consequence of vascular dys-

regulation are thought to cause intermittent ischemia, thereby damaging retinal ganglion cells by ischemia-reperfusion injury.

So it is safe to say, that there is still a fierce debate in the field of glaucoma research as to what the mechanisms causing or contributing to the development and progression of glaucomatous optic nerve damage are.

The optic nerve microenvironment

Most research into the causes for glaucomatous damage to the optic nerve is focused on processes taking place in the eye. However, the visual system and the damage caused by glaucoma extend well beyond the eye and include the optic nerve as well. As part of the brain, the optic nerve is enveloped by the meninges that provide barrier function and protect the central nervous system. The meninges consist of three layers – the dura, arachnoid and pia mater. Meningothelial cells or MECs cover the meninges and thus form the interface between the cerebro-spinal fluid (CSF) and the rest of the body. The optic nerve sheath is anatomically a peculiar area. It is an extension of the CSF-filled column around the brain matter formed like a cul-de-sac. This has certain implications for the flow of CSF and its renewal. It has long been known that the CSF does not only provide a cushion for the brain but that the CSF is also central in transporting nutrients, waste products and hormones and is also the site of immunological reactions. Thus, CSF turnover is essential for its function with the choroid plexus producing around 500 ml of this special liquid, renewing the CSF three times daily. Due to the peculiar anatomy of the optic nerve microenvironment, renewal of the CSF around the optic nerve faces particular problems. While CSF can freely enter this area, leaving this area is not possible through the same route. And indeed, lymphatic canals were found near the optic nerve implicated in CSF drainage. Now, clinical observations made in patients suffering from papilledema and normal tension glaucoma demonstrate a clear compartmentalization of the CSF around the optic nerve from the rest of the CSF volume associated with elevated pressure inside this compartment. Interestingly, fenestration of the optic nerve is able to release this build-up pressure and reverses the compartmentalization with patients experiencing improvement of their

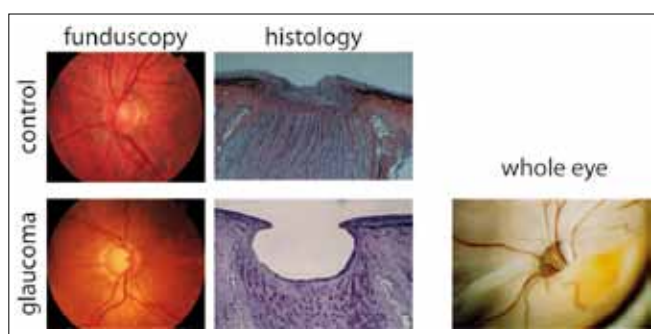


Figure 2: Glaucomatous damage. A funduscopy reveals a characteristic alteration of the papilla. Histological analysis illustrates the drastic loss of retinal ganglion cells and the tissue remodelling in the optic nerve head area. The post-mortem whole eye picture nicely demonstrates the so called cupping of the optic nerve head.

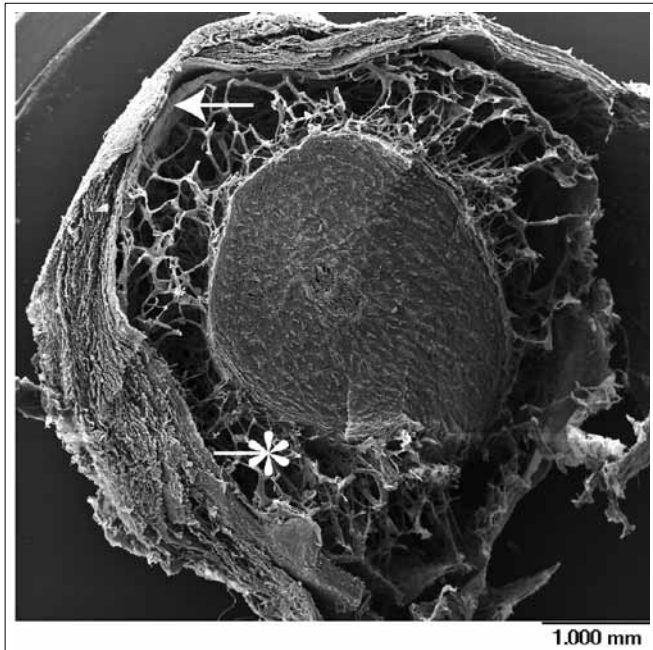


Figure 3: Microenvironment of the optic nerve. Shown is an electron microscopic picture of a cross section of an optic nerve. From the outside to the inside: dura mater, arachnoid mater (arrow), trabeculae and septae of the subarachnoid space (asterisk) and pia mater surrounding the axon bundle forming the actual optic nerve.

visual defects. Considering the confinement of the optic nerve surroundings and the intricate architecture of MECs forming a maze of trabeculae and septae (Figure 3), one can easily imagine that tissue remodelling in this area can alter or obstruct the flow of CSF with potential detrimental consequences for optic nerve function. Through the analysis of post-mortem optic nerves of glaucoma patients we found significant changes in the microenvironment of the optic nerve. And since MECs form this microenvironment, we focused our efforts on understanding MECs and their potential role in diseases of the optic nerve including glaucoma but also other neurodegenerative disorders.

Although MECs seem to exert an important function in protecting the brain, these cells are barely studied and their interactions with the CSF compartment are mainly uncharted. To study MECs, we established a primary cell culture from porcine optic nerve sheaths we obtain fresh from the slaughterhouse in Basel. [Off note, these eyes are of the highest quality and find many uses in our laboratory and we are sure the remainder of these pigs have equally important (and delicious) applications.] We also use MECs derived from an immortalized benign, human meningioma for our work. While study-

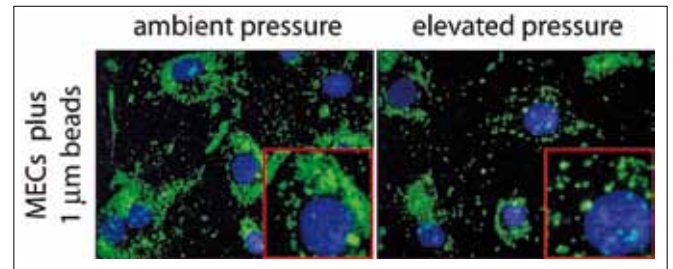


Figure 4: Elevated pressure affects MEC phagocytosis. Elevated (30 mmHg) and atmospheric pressure treated MECs were incubated with fluorescently labelled latex beads, fixed, DAPI stained and analyzed by microscopy. Bead uptake is significantly inhibited in MECs treated with elevated pressure compared to control cells.

ing MECs, we found that these cells react to elevated pressure. When we applied atmospheric pressure + 30 mmHg, MECs increased their proliferation by around 20%. In addition, MECs seem to provide clearance function for the CSF. MECs perform quite a lot of phagocytosis and pinocytosis; considering the huge area covered by these cells this might be a route for the removal of waste products. Interestingly, while elevated pressure caused increased proliferation of these cells, their phagocytotic activity was diminished by this treatment (Figure 4). Another culprit connected to neurodegenerative disorders is oxidative stress. While MECs show high resistance to oxidative stress inducing agents in terms of viability, their ability to phagocytose is severely affected by such treatments.

This lead us to propose a vicious circle of increased MEC proliferation leading to changes in the architecture of the optic nerve microenvironment causing altered CSF renewal which in turn puts additional stress on MECs and negatively affects their ability to phagocytose and perform their CSF clearing function. One can then imagine that not well maintained CSF might have a negative influence on optic nerve function.

Recently, we also discovered a potential immunological function for MECs in the CSF. We found that MECs are active producers of cytokines in response to various stimuli associated with bacterial infection. In addition, their phagocytic and pinocytic activity was enhanced after stimulation with lipopolysaccharide further supporting a CSF clearing function for MECs.

Future directions for our research into MECs will entail a more thorough analysis of MECs in terms of their barrier function in vivo using immunohistochemistry and

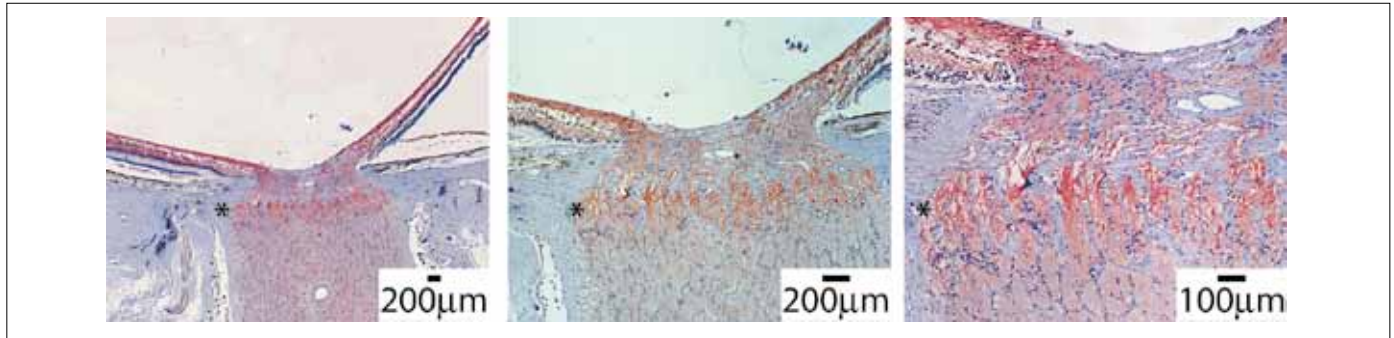


Figure 5: Mitochondrial distribution in the optic nerve. The mitochondrial marker COX IV was stained in a cross section of a human eye. Note the strong staining in the retina and the optic nerve head (*) compared to the remainder of the optic nerve. While the axons in the optic nerve are myelinated, due to space and optical restraints no myelin is present in the retina and the optic nerve head, thus causing high energy demand for signal propagation in the absence of nodes of Ranvier.

human optic nerve samples as well as changes in MEC architecture in other diseases of the optic nerve associated with the death of retinal ganglion cells.

Mitochondrial health and neurodegeneration

Despite all controversy about its aetiology – high and normal pressure, mechanistic and biochemical explanations, vascular dysregulation or optic nerve microenvironment – glaucoma is at the core a neurodegenerative disorder. The loss of vision is ultimately caused by the untimely death of retinal ganglion cells that form the optic nerve with their around one million axons. Central to most if not all neurodegenerative disorders is the involvement of mitochondria respectively their dysfunction. Thus, we concentrate our efforts to better understand how mitochondria are kept in shape and how dysfunctional mitochondria are connected to cell death and neurodegeneration especially during glaucoma. Mitochondria are multitaskers. They are involved in lipid metabolism, the production of iron-sulphur clusters, the storage of calcium ions and are executioners of

programmed cell death, but first and foremost they are the major producer of ATP in the process of oxidative phosphorylation. Due to the high energy demand of neuronal cells, neurons depend on oxidative phosphorylation and cannot rely on glycolysis alone to meet their ATP demands. This is especially true for the eye (Figure 5). Since these organelles handle oxygen, a quite toxic substance, oxidative damage to mitochondrial DNA and proteins is quasi an occupational hazard. And damaged mitochondria are not only not efficient in ATP production but are also producers of potentially dangerous reactive oxygen species (ROS) such as superoxide. Thus, mitochondria have to be maintained in order to keep cellular ATP levels high and to prevent excessive ROS production and therefore oxidative damage. Failure to do so might ultimately result in neurodegeneration. Maintaining mitochondria is a three tiered process (Figure 6). At the molecular level, bacterial type proteases located in the matrix of mitochondria are responsible for the removal of oxidized proteins, while AAA proteases anchored in the inner mitochondrial membrane

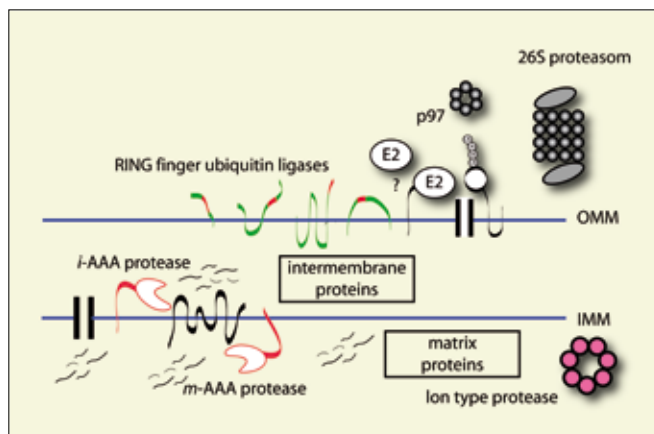


Figure 6: Different proteolytic systems are active in the four mitochondrial compartments. Quality control in the matrix is performed by Lon and ClpX, proteins related to bacterial proteases dating back to the endosymbiotic event that formed modern eukaryotic cells some 1.5 billion years ago. The inner mitochondrial membrane harbours AAA proteases facing the matrix (m-AAA) and the intermembrane space (i-AAA). Recent data from us and others point to a role of membrane-anchored RING finger ubiquitin ligases in the turnover of OMM proteins in a process we dubbed OMMAD for outer mitochondrial membrane associated degradation; a process that is related to ER associated degradation (ERAD) responsible for quality control in the endoplasmic reticulum.

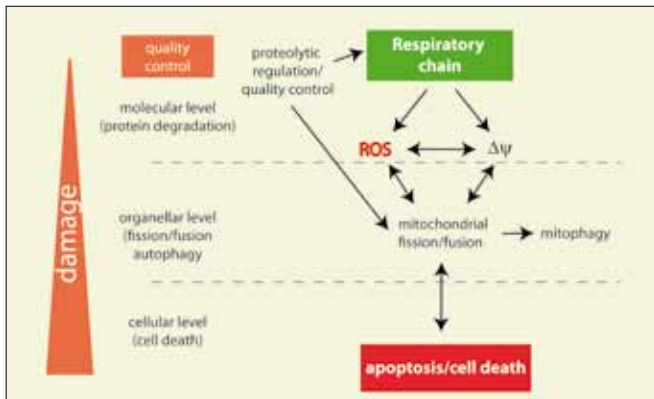


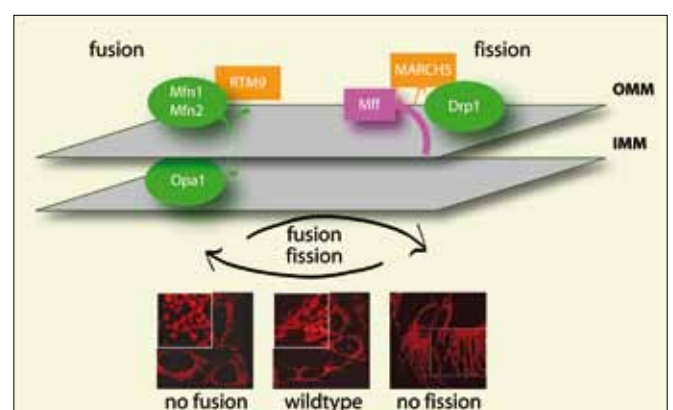
Figure 7: The central role of mitochondrial morphology regulation. All three levels of mitochondrial quality control are influenced by mitochondrial morphology. In turn, the mitochondrial network adapts as well with the ultimate goal to keep the respiratory chain running efficiently and therefore to keep ATP production high.

(IMM) degrade IMM-localized membrane proteins. Additional mitochondrial quality control is performed through ubiquitin-proteasome dependent degradation of proteins of the outer mitochondrial membrane (OMM) by specialized OMM-localized ubiquitin ligases. The second tier of mitochondrial maintenance is at the organellar level. In a process termed mitophagy, entire, non-functional mitochondrial subunits are removed by autophagy. Interestingly, recent work revealed a role for the ubiquitin ligase Parkin, a gene mutated in familial Parkinson's disease, in the autophagic destruction of damaged, depolarized mitochondria. These findings provide another link between mitochondrial dysfunction/quality control and neurodegenerative disorders. The third tier of mitochondrial maintenance takes place at the cellular level. Mitochondria are an integral part of the apoptotic machinery. The release of cytochrome c from the mitochondrial intermembrane space (IMS) is the point of no-return for the induction of programmed cell death. Thus, extensive damage to the mitochondrial network causes apoptotic cell death removing an entire mitochondrial network in an ultimate quality control process. These three mechanisms are interdependent

(Figure 7) and connected through regulators of mitochondrial morphology (Figure 8).

Unlike the classical textbook picture of rather small, uninteresting looking, bean shaped objects, mitochondria are very dynamic organelles and quite beautiful to look at (Figure 9). In fact, mitochondria form vast networks inside most cells that are shaped by constant ongoing fission and fusion of mitochondrial tubules. Recent advances in the understanding of this process revealed this integrative role of mitochondrial morphology. Mitochondrial fission is an important part of the apoptotic program. During the release of cytochrome c from the IMS, mitochondria fragment and it was shown that the inhibition of this fragmentation inhibits the progression of programmed cell death. And the opposite is true for mitochondrial fusion: interference with the fusion machinery sensitizes cells to apoptotic stimuli. On the other hand, proteins known for their pro-apoptotic function such as BAX and BAK are now acknowledged for their role in morphology regulation in healthy cells. Mitochondrial fragmentation does not only play a role in programmed cell death; during mitophagy, shortening of mitochondria greatly aids the uptake of damaged

Figure 8: The mitochondrial fission and fusion machineries. Mitochondrial morphology is maintained by large GTPases (in green). Fission is performed by the dynamin-related Drp1 together with the docking factor Mff, while fusion of the outer and inner mitochondrial membrane is achieved by the mitofusins (Mfn1 and Mfn2) and Opa1, respectively. Both processes are influenced by two novel mitochondrial ubiquitin ligases (in orange), MARCH5 and RTM9. For the microscopic images, cells were stained for the mitochondrial marker cytochrome c illustrating a wildtype mitochondrial network (middle panel), fragmented mitochondria due to deletion of a mitofusin (left panel) and highly interconnected mitochondria following knockdown of the fission protein Drp1 (right panel).



subunits into autophagosomes. But changes in mitochondrial morphology are also important for the repair of minor damage. Mixing of the matrix content of two mitochondrial tubules is thought to provide templates for mtDNA repair. And since mitochondrial fusion depends on the presence of a mitochondrial membrane potential in both partners, continuous fusion provides a means of weeding out damaged and depolarized mitochondrial subunits.

The central role of mitochondrial morphology is highlighted by various diseases associated with mitochondrial morphogens. Mutations in the fusion protein Opa1 cause dominant optic atrophy (DOA), the most common hereditary optic neuropathy. [In a genealogical side note, there is also a mitochondrial Oma1 (German for grandma 1), that is involved in the proteolytic processing of Opa1 (German for grandpa 1).] Another neurodegenerative disorder associated with a mitochondrial morphogen is Charcot-Marie-Tooth 2A (CMT2A), where mutations in the mitofusin Mfn2 cause a peripheral neuropathy that is combined in some cases with an optic neuropathy and impaired hearing. Interestingly, no hereditary disease is associated with mutations of the central fission protein Drp1, however, a rare, lethal birth defect was reported that seemed to be caused by non-functional Drp1. While mutations in Drp1 seem to be mostly detrimental, MARCH5, a mitochondrial ubiquitin ligase and regulator of Drp1, was recently implicated in the degradation of mSOD1, connected to amyotrophic lateral sclerosis, and to the turnover of ataxin-3 polyQ, associated with Machado-Joseph disease. This further connects the mitochondrial fission machinery to neurodegenerative processes much like it was shown for the fusion machinery before.

Our work now focuses on the characterization of the mitochondrial ubiquitin ligases MARCH5 and RTM9 and their role in protein turnover and mitochondrial quality control. In addition, we employ an *in vitro* model of retinal ganglion cells (RGCs) to study the effect of modulating mitochondrial morphology and protein turnover on the survival of RGCs. So far, we identified an important role for RTM9 in keeping mitochondria functional and in shape. In addition, we found that MARCH5 is involved in the mitochondrial morphology changes in RGCs in response to elevated pressure. While mitochondria frag-

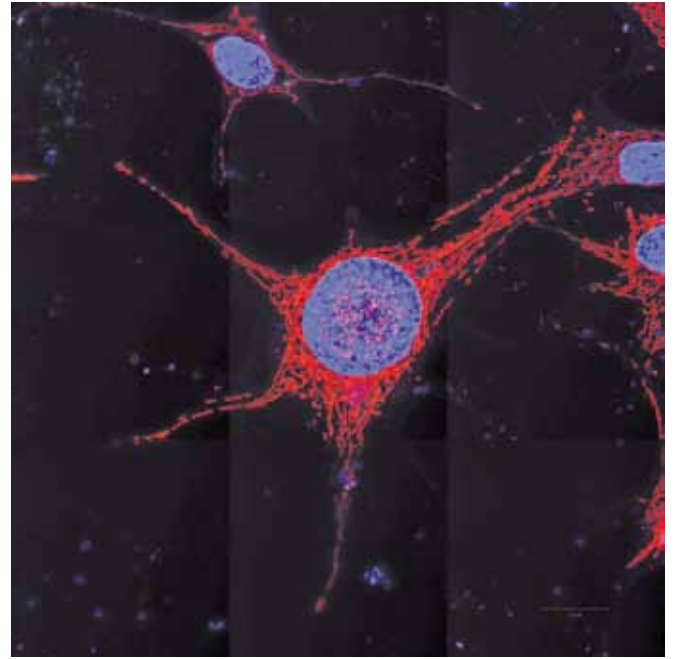


Figure 9: Mitochondrial network. A differentiated retinal ganglion cell (RGC5) was stained against the mitochondrial marker cytochrome c to highlight the mitochondrial network. The image was taken on the LSM710 Meta with a 63x objective lens using 0.5 μm sectioning and 3x3 tiling.

ment and thus most likely sensitize RGCs to apoptotic stimuli, inactivation of MARCH5 interferes with this process and might have a protective function.

While there still remain many open questions regarding glaucoma, we hope that our integrative approach will lead to more insight into the aetiology of this blinding disease. Beyond that, insight into the molecular mechanisms leading to glaucomatous neurodegeneration might prove useful for the understanding of other such diseases.

Acknowledgements: We would like to acknowledge our collaboration partners, Prof. Hanspeter Killer (Kantonsspital Aarau), Prof. Mariusz Karbowski (University of Maryland, Baltimore, Maryland, USA) and Richard Youle (National Institutes of Health, Bethesda, Maryland, USA) Also, we would like to thank our sources of funding, the Swiss National Foundation, the “Messerli Stiftung”, the “Gottfried und Julia Bangerter-Rhyner Stiftung” and the “Grieshaber Stiftung für Augenforschung” for their support.

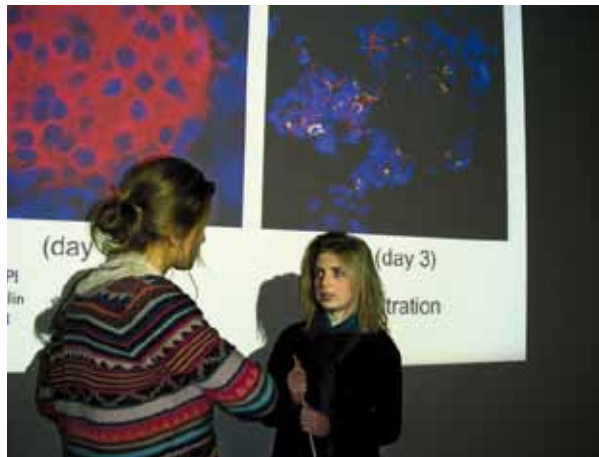
Albert Neutzner



This year we decided to start the PhD Club again. The PhD Club is a platform to for present and discuss ideas, open to all PhD students no matter whether they are at the beginning or at the end of their thesis.

Who doesn't get nervous and lose sleep before giving a first talk in front of a big audience? Although many students have had some experience presenting papers to fellow students during lecture at university, presenting one's own data means something different. Since the club is only open to students, the students are the experts, and as such, are responsible for generating and interpreting the data they present. The main benefit of the PhD Club is that it gives all PhD students the opportunity to share their data in a relaxed environment where they can discuss implications, ideas and problems. Moreover, they receive helpful input from students with different specializations and insight - shining light on the project from a different point of view.

During undergraduate studies many students were accus-



tomed to sitting in the lecture hall and waiting for information given by the professor at the front. Asking questions was embarrassing because the student worried that the question might be stupid, or that other students and possibly even the Professor might think the student is stupid. For the participants of the PhD club, we provide the opportunity to ask questions and to overcome self-doubt.

Apart from presenting results and asking questions there are many other concerns that PhD students find themselves confronted with including but not limited to project mapping, time management, problem solving, literature searches and writing. These and many other things are also discussed in the PhD Club.

Last, but not least, the Aperó at the end of a presentation and the summer activities are a good opportunity to social network. We hope that more students will read this article and become curious and motivated to join the PhD Club !

Sabrina Köhli

Dissertationen

Am 28. Februar 2011 stellte sich **Stefanie Fritz** von der Forschungsgruppe Immunobiology (Departement Biomedizin USB) dem Dissertationskomitee. Der Titel ihrer Dissertation lautete: "Influenza vaccination in immunocompromised patients/The role of regulatory NK cells".

Seit dem 25. März 2011 darf sich **Berit Rosc** von der Forschungsgruppe Myocardial Research (Departement Biomedizin USB) Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "NADPH oxidase (NOX) in the heart: The interplay of NOX-derived ROS in β 1-integrin-induced survival signalling".

Am 28. März 2011 stellte sich **Ramin Radpour** von der Forschungsgruppe Gynecological Oncology (Departement Biomedizin USB) dem Dissertationskomitee. Der Titel seiner Dissertation lautete: "Epigenetic and genomic biomarker discovery in breast cancer".

Mit der Doktorprüfung am 15. April 2011 schloss **Daniel Meier** von der Forschungsgruppe Diabetes Research (Departement Biomedizin USB) erfolgreich seine Dissertationszeit ab. Das Thema seiner Doktorarbeit lautete: "On the Role of TLR2 and SIRT1 in the Development of Diabetes Mellitus".

Beförderungen

Irene Hösli wird Extraordinaria für Geburtshilfe

Irene Hösli von der Forschungsgruppe Prenatal Medicine (Departement Biomedizin USB) wurde vom Universitätsrat in seiner Sitzung am 26. Mai 2011 zur Extraordinaria für Geburtshilfe an der Medizinischen Fakultät der Universität Basel ernannt. Gleichzeitig wurde sie zur Chefärztin an der Frauenklinik des Universitätsspitals Basel gewählt.

Jürg Schwaller zum Extraordinarius für Kindliche Leukämien ernannt

Jürg Schwaller von der Forschungsgruppe Childhood Leukemia (Departement Biomedizin USB) wurde vom

Universitätsrat in seiner Sitzung vom 23. Juni 2011 zum Extraordinarius für Kindliche Leukämien an der Medizinischen Fakultät der Universität Basel ernannt. Jürg Schwaller war bereits bisher als Forschungsgruppenleiter des Labors Childhood Leukemia im Rahmen seiner Professur der Gertrude-von-Meissner-Stiftung für kindliche Leukämien tätig.

Herzliche Gratulation an alle!

Selected publications by DBM members

Below you can find the abstracts of recent articles published by members of the DBM. The abstracts are grouped according to the impact factor of the journal where the work appeared. To be included, the papers must meet the following criteria:

1. The first author, last author or corresponding author (at least one of them) is a member of the DBM.
2. The DBM affiliation must be mentioned in the authors list as it appeared in the journal.
3. The final version of the article must be available (online pre-publications will be included when the correct volume, page numbers etc. becomes available).

We are primarily concentrating on original articles. Due to page constraints, abstracts of publications that appeared in lower ranked journals may not be able to be included. Review articles are generally not considered, unless they appeared in the very top journals (e.g. Cell, Science, Nature, NEJM, etc.). The final decision concerning inclusion of an abstract will be made by the chair of the Department of Biomedicine.

If you wish that your article will appear in the next issue of DBM Facts please submit a pdf file to the Departmental Assistant, Manuela Bernasconi: manuela.bernasconi@unibas.ch

Deadline for the next issue is July 31, 2011.

Cardiac Raptor Ablation Impairs Adaptive Hypertrophy, Alters Metabolic Gene Expression, and Causes Heart Failure in Mice

Pankaj Shende, MSc; Isabelle Plaisance, PhD; Christian Morandi, MSc; Corinne Pellioux, PhD; Corinne Berthonneche, PhD; Francesco Zorzato, MD; Jaya Krishnan, PhD; René Lerch, MD; Michael N. Hall, PhD; Markus A. Rüegg, PhD; Thierry Pedrazzini, PhD; Marijke Brink, PhD

Abstract:

Background—Cardiac hypertrophy involves growth responses to a variety of stimuli triggered by increased workload. It is an independent risk factor for heart failure and sudden death. Mammalian target of rapamycin (mTOR) plays a key role in cellular growth responses by integrating growth factor and energy status signals. It is found in 2 structurally and functionally distinct multiprotein complexes called mTOR complex (mTORC) 1 and mTORC2. The role of each of these branches of mTOR signaling in the adult heart is currently unknown.

Methods and Results—We generated mice with deficient myocardial mTORC1 activity by targeted ablation of *raptor*, which encodes an essential component of mTORC1, during adulthood. At 3 weeks after the deletion, atrial and brain natriuretic peptides and β -myosin heavy chain were strongly induced, multiple genes involved in the regulation of energy metabolism were altered, but cardiac function was normal. Function deteriorated rapidly afterward, resulting in dilated cardiomyopathy and high mortality within 6 weeks. Aortic banding–induced pathological overload resulted in severe dilated cardiomyopathy already at 1 week without

a prior phase of adaptive hypertrophy. The mechanism involved a lack of adaptive cardiomyocyte growth via blunted protein synthesis capacity, as supported by reduced phosphorylation of ribosomal S6 kinase 1 and 4E-binding protein 1. In addition, reduced mitochondrial content, a shift in metabolic substrate use, and increased apoptosis and autophagy were observed.

Conclusions—Our results demonstrate an essential function for mTORC1 in the heart under physiological and pathological conditions and are relevant for the understanding of disease states in which the insulin/insulin-like growth factor signaling axis is affected such as diabetes mellitus and heart failure or after cancer therapy.

From the Department of Biomedicine, University of Basel and University Hospital Basel, Basel, Switzerland (P.S., I.P., C.M., F.Z., M.B.); Medical Research Foundation and Cardiology Division, University of Geneva and University Hospital Geneva, Geneva, Switzerland (C.P., R.L.); Cardiovascular Assessment Facility, University of Lausanne Medical School, Lausanne, Switzerland (C.B.); Department of Medicine, University of Lausanne Medical School, Lausanne, Switzerland (T.P.); ETH Zurich, Zurich, Switzerland (J.K.); and Biozentrum, University of Basel, Basel (M.N.H., M.A.R.), Switzerland. Dr Plaisance's current affiliation is Department of Medicine, University of Lausanne Medical School, Lausanne, Switzerland.

Interferon-Induced Gene Expression Is a Stronger Predictor of Treatment Response Than *IL28B* Genotype in Patients With Hepatitis C

Michael T. Dill,^{1,4} François H. T. Duong,¹ Julia E. Vogt,² Stéphanie Bibert,⁶ Pierre-Yves Bochud,⁶ Luigi Terracciano,⁵ Andreas Papassotiropoulos,³ Volker Roth,² and Markus H. Heim^{1,4}

Abstract:

Background & Aims: The host immune response during the chronic phase of hepatitis C virus infection varies among individuals; some patients have a no interferon (IFN) response in the liver, whereas others have full activation of IFN-stimulated genes (ISGs). Preactivation of this endogenous IFN system is associated with nonresponse to pegylated IFN- α (pegIFN- α) and ribavirin. Genome-wide association studies have associated allelic variants near the *IL28B* (*IFN λ 3*) gene with treatment response. We investigated whether *IL28B* genotype determines the constitutive expression of ISGs in the liver and compared the abilities of ISG levels and *IL28B* genotype to predict treatment outcome.

Methods: We genotyped 109 patients with chronic hepatitis C for *IL28B* allelic variants and quantified the hepatic expression of ISGs and of *IL28B*. Decision tree ensembles, in the form of a random forest classifier, were used to calculate the relative predictive power of these different variables in a multivariate analysis.

Results: The minor *IL28B* allele was significantly associated with increased expression of ISG. However, stratification of the patients according to treatment response revealed increased ISG expression in nonresponders, irrespective of *IL28B* genotype. Multivariate analysis of ISG expression, *IL28B* genotype, and several other factors associated with response to therapy identified ISG expression as the best predictor of treatment response.

Conclusions: *IL28B* genotype and hepatic expression of ISGs are independent predictors of response to treatment with pegIFN- α and ribavirin in patients with chronic hepatitis C. The most accurate prediction of response was obtained with a 4-gene classifier comprising *IFI27*, *ISG15*, *RSAD2*, and *HTATIP2*.

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Interferon- β and Interferon- λ Signaling Is Not Affected by Interferon-Induced Refractoriness to Interferon- α *In Vivo*

Zuzanna Makowska,¹ Francois H. T. Duong,¹ Gaia Trincucci,¹ David F. Tough,² and Markus H. Heim^{1,3}

Abstract:

Therapy of chronic hepatitis C with pegylated interferon α (pegIFN- α) and ribavirin achieves sustained virological responses in approximately half of the patients. Nonresponse to treatment is associated with constitutively increased expression of IFN-stimulated genes in the liver already before therapy. This activation of the endogenous IFN system could prevent cells from responding to therapeutically injected (peg)IFN- α , because prolonged stimulation of cells with IFN- α induces desensitization of the IFN signal transduction pathway. Whether all types of IFNs induce refractoriness in the liver is presently unknown. We therefore treated mice with multiple injections and different combinations of IFN- α , IFN- β , IFN- γ , and IFN- λ . Pretreatment of mice with IFN- α , IFN- β , and IFN- λ induced a strong expression of the negative regulator ubiquitin-specific peptidase 18 in the liver and gut. As a result, IFN- α signaling was significantly reduced

when mice were reinjected 16 hours after the first injection. Surprisingly, both IFN- β and IFN- λ could activate the Janus kinase-signal transducer and activator of transcription (STAT) pathway and the expression of IFN-stimulated genes despite high levels of ubiquitin-specific peptidase 18. IFN- λ treatment of human liver biopsies *ex vivo* resulted in strong and maintained phosphorylation of STAT1, whereas IFN- α -induced STAT1 activation was transient.

Conclusion: Contrary to the action of IFN- α , IFN- β , and IFN- λ signaling in the liver does not become refractory during repeated stimulation of the IFN signal transduction pathway. The sustained efficacy of IFN- β and IFN- λ could be an important advantage for the treatment patients who are nonresponders to pegIFN- α , through a preactivated endogenous IFN system.

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Antigen-Specific Adaptive Immune Responses in Fingolimod-Treated Multiple Sclerosis Patients

Matthias Mehling, MD^{1,2}, Patricia Hilbert, MD¹, Stefanie Fritz, MSc², Bojana Durovic, MD, PhD², Dominik Eichin, BSc², Olivier Gasser, PhD², Jens Kuhle, MD¹, Thomas Klimkait, PhD³, Raija L.P. Lindberg, PhD¹, Ludwig Kappos, MD¹, Christoph Hess, MD, PhD²

Abstract:

T cells exit secondary lymphoid organs along a sphingo-sine1-phosphate (S1P) gradient and, accordingly, are reduced in blood upon fingolimod-mediated S1P-receptor (S1PR)-blockade. Serving as a model of adaptive immunity, we characterized cellular and humoral immune responses to influenza vaccine in fingolimod-treated patients with multiple sclerosis (MS) and in untreated healthy controls. Although the mode of action of fingolimod might predict reduced immunity, vaccine-triggered T cells accumulated normally in blood despite efficient S1PR-blockade. Concentrations of anti-influenza A/B immunoglobulin (Ig)M and IgG also increased similarly in both groups. These results indicate that fingolimod-treated individuals can mount vaccine-specific adaptive immune responses comparable to healthy controls.

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Neurofilament heavy chain in CSF correlates with relapses and disability in multiple sclerosis

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Abstract:

Objective: Neurodegeneration is now accepted as a pathologic hallmark of multiple sclerosis (MS). We sought to discover whether CSF levels of neurofilament heavy chain protein (NfH^{SMI35}) correlate with disability, disease activity, or specific stages of MS.

Methods: An electrochemiluminescence immunoassay was used to retrospectively measure NfH^{SMI35} in CSF of patients with clinically isolated syndrome (CIS) (n = 63), relapsing-remitting multiple sclerosis (RRMS) (n = 39), secondary progressive multiple sclerosis (SPMS) (n = 25), primary progressive multiple sclerosis (PPMS) (n = 23), or controls (n = 73). Cell count and CSF levels of immunoglobulin and albumin were also measured.

Results: CSF levels of NfH^{SMI35} increased with age in controls ($r_s = 0.50$, $p < 0.0001$) and CIS ($r_s = 0.50$, $p < 0.0001$); this effect was less pronounced in RRMS ($r_s = 0.35$, $p = 0.027$) and absent in SPMS/PPMS. After age correction, NfH^{SMI35} levels were found to be higher in all disease stages compared to control. Relapses were associated with higher CSF NfH^{SMI35} values

compared with stable disease. NfH^{SMI35} levels correlated with EDSS scores in patients with CIS and RRMS ($r_s = 0.33$, $p = 0.001$), and during relapse ($r_s = 0.35$, $p = 0.01$); the correlation was most prominent in RRMS during relapse ($r_s = 0.54$, $p = 0.01$). This was not the case for any of the other CSF markers examined.

Conclusions: Neuronal loss is a feature of aging, and the age-dependent increase of CSF NfH^{SMI35} suggests that this loss accelerates over time. For MS, increased NfH^{SMI35} levels reflect the superimposed presence of further neurodegenerative processes. Evaluation of NfH^{SMI35} levels is likely to provide a useful surrogate for measuring the rate of neurodegeneration in MS. Furthermore, the dissociation of NfH^{SMI35} levels with biomarkers of inflammation suggests that the mechanisms responsible for their production are at least partly independent.

From Clinical Neuroimmunology, Departments of Biomedicine and Neurology (J.K., D.L., M.M., L.K., R.L.P.L.), Laboratory Medicine (A.R.), and Institute for Social and Preventive Medicine (C.S.), University Hospital Basel, Basel, Switzerland; UCL Institute of Neurology (A.P.), Department of Neuroimmunology, Queen Square, London, UK; Department of Neurology (A.P.), Free University Medical Center, Amsterdam, the Netherlands; and Department of Pharmacology (D.C.A.), University of Oxford, UK.

Development

Development
dev.biologists.org

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IF 7.1

SHH propagates distal limb bud development by enhancing CYP26B1-mediated retinoic acid clearance via AER-FGF signalling

Simone Probst¹, Conradin Kraemer², Philippe Demougin³, Rushikesh Sheth^{1*}, Gail R. Martin⁴, Hidetaka Shiratori⁵, Hiroshi Hamada⁵, Dagmar Iber², Rolf Zeller¹ and Aimée Zuniga^{1†}

Summary

The essential roles of SHH in anteroposterior (AP) and AER-FGF signalling in proximodistal (PD) limb bud development are well understood. In addition, these morphoregulatory signals are key components of the self-regulatory SHH/GREM1/AER-FGF feedback signalling system that regulates distal progression of limb bud development. This study uncovers an additional signalling module required for coordinated progression of limb bud axis development. Transcriptome analysis using *Shh*-deficient mouse limb buds revealed that the expression of proximal genes was distally extended from early stages onwards, which pointed to a more prominent involvement of SHH in PD limb axis development. In particular, retinoic acid (RA) target genes were upregulated proximally, while the expression of the RA-inactivating *Cyp26b1* enzyme was downregulated distally, pointing to increased RA activity in *Shh*-deficient mouse limb buds. Further genetic and molecular analysis established that *Cyp26b1* expression is regulated by AER-FGF signalling. During initiation of limb bud outgrowth, the activation of *Cyp26b1* expression creates a distal 'RA-free' domain, as indicated by complementary downregulation of a transcriptional sensor of RA activity. Subsequently, *Cyp26b1* expression

increases as a consequence of SHH-dependent upregulation of AER-FGF signalling. To better understand the underlying signalling interactions, computational simulations of the spatiotemporal expression patterns and interactions were generated. These simulations predicted the existence of an antagonistic AER-FGF/CYP26B1/RA signalling module, which was verified experimentally. In summary, SHH promotes distal progression of limb development by enhancing CYP26B1-mediated RA clearance as part of a signalling network linking the SHH/GREM1/AER-FGF feedback loop to the newly identified AER-FGF/CYP26B1/RA module.

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Human Mutation

Human Mutation

32:309-317, 2011

IF 6.8

Alterations of Excitation–Contraction Coupling and Excitation Coupled Ca²⁺ Entry in Human Myotubes Carrying *CAV3* Mutations Linked to Rippling Muscle Disease

Nina D. Ullrich¹, Dirk Fischer^{2,3}, Cornelia Kornblum⁴, Maggie C. Walter⁵, Ernst Niggli¹, Francesco Zorzato^{6,7}, and Susan Treves^{6,7}

Abstract:

Rippling muscle disease is caused by mutations in the gene encoding caveolin-3 (*CAV3*), the muscle-specific isoform of the scaffolding protein caveolin, a protein involved in the formation of caveolae. In healthy muscle, caveolin-3 is responsible for the formation of caveolae, which are highly organized sarcolemmal clusters influencing early muscle differentiation, signalling and Ca²⁺ homeostasis. In the present study we examined Ca²⁺ homeostasis and excitation–contraction (E-C) coupling in cultured myotubes derived from two patients with Rippling muscle disease with severe reduction in caveolin-3 expression; one patient harboured the heterozygous c.84C>A mutation while the other patient harbored a homozygous splice-site mutation (c.102+ 2T>C) affecting the splice donor site of intron 1 of the *CAV3* gene. Our results show that

cells from control and rippling muscle disease patients had similar resting [Ca²⁺]_i and 4-chloro-*m*-cresol-induced Ca²⁺ release but reduced KCl-induced Ca²⁺ influx. Detailed analysis of the voltage-dependence of Ca²⁺ transients revealed a significant shift of Ca²⁺ release activation to higher depolarization levels in *CAV3* mutated cells. High resolution immunofluorescence analysis by Total Internal Fluorescence microscopy supports the hypothesis that loss of caveolin-3 leads to microscopic disarrays in the colocalization of the voltage-sensing dihydropyridine receptor and the ryanodine receptor, thereby reducing the efficiency of excitation–contraction coupling.

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A Systematic Search for Endoplasmic Reticulum (ER) Membrane-associated RING Finger Proteins Identifies Nixin/ZNRF4 as a Regulator of Calnexin Stability and ER Homeostasis

Albert Neutzner^{1,2}, Melanie Neutzner^{2,3}, Anne-Sophie Benischke², Seung-Wook Ryu^{1,4}, Stephan Frank³, Richard J. Youle¹, and Mariusz Karbowski^{1,5}

Abstract:

To identify novel regulators of endoplasmic reticulum (ER)-linked protein degradation and ER function, we determined the entire inventory of membrane-spanning RING finger E3 ubiquitin ligases localized to the ER. We identified 24 ER membrane-anchored ubiquitin ligases and found Nixin/ZNRF4 to be central for the regulation of calnexin turnover. Ectopic expression of wild type Nixin induced a dramatic down-regulation of the ER-localized chaperone calnexin that was prevented by inactivation of the Nixin RING domain. Importantly, Nixin physically interacts with calnexin in a glycosylation-independent manner, induces calnexin ubiquitination, and p97-dependent degradation, indicating an ER-associated degradation-like mechanism of calnexin turnover.

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CMX001 (1-O-Hexadecyloxypropyl-Cidofovir) Inhibits Polyomavirus JC Replication in Human Brain Progenitor-Derived Astrocytes

Rainer Gosert¹, Christine Hanssen Rinaldo², Marion Wernli¹, Eugene O. Major³, and Hans H. Hirsch^{1,4}

Abstract:

Polyomavirus JC (JCV) replication causes progressive multifocal leukoencephalopathy (PML), a frequently fatal brain disease in immunodeficient patients, yet antiviral drugs are lacking. We characterized the lipid conjugate 1-O-hexadecyloxypropyl-cidofovir (CMX001) regarding JCV (Mad-4) replication in human brain progenitor-derived astrocytes (PDA) and the simian virus 40 (SV40) large-T-antigen-expressing COS-7 cells up to 7 days postinfection (dpi). We examined JCV loads by PCR, the infection rate by immunofluorescence, and host cell toxicity by WST-1 and BrdU incorporation assays. Supernatants from CMX001-treated PDA demonstrated a drug concentration-dependent decrease in JCV loads and infectivity.

CMX001 had only a modest effect on host cell metabolism but reduced overall BrdU incorporation. In PDA at 7 dpi, the CMX001 50% effective concentration (EC₅₀) was 5.55 nM, the 50% cytotoxic concentration (CC₅₀) was 184.6 nM, and the 50% selectivity index (SI₅₀) was 33.3. The EC₉₀ was 19.7 nM, the CC₉₀ was 5,054 nM, and the SI₉₀ was 256.1. In COS-7 cells, JCV replication was faster and the EC₅₀ and EC₉₀ were 18- and 37-fold higher than those in PDA, i.e., 0.1 μM and 0.74 μM (CC₅₀, 0.67 μM; SI₅₀, 6.7; CC₉₀, 12.2 μM; SI₉₀, 16.5) at 5 dpi. We conclude that CMX001 inhibits JCV replication at concentrations *in vitro* that can be attained by oral administration without significant side effects in clinical studies.

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Plos One

PLOS one

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Hes1 Is Required for Appropriate Morphogenesis and Differentiation during Mouse Thyroid Gland Development

Aurore Carre¹, Latif Rachdi¹, Elodie Tron¹, Bénédicte Richard¹, Mireille Castanet¹, Martin Schlumberger², Jean-Michel Bidart³, Gabor Szinnai^{4,5,*}, Michel Polak^{1,6,*}

Abstract:

Notch signalling plays an important role in endocrine development, through its target gene *Hes1*. *Hes1*, a bHLH transcriptional repressor, influences progenitor cell proliferation and differentiation. Recently, *Hes1* was shown to be expressed in the thyroid and regulate expression of the sodium iodide symporter (*Nis*). To investigate the role of *Hes1* for thyroid development, we studied thyroid morphology and function in mice lacking *Hes1*. During normal mouse thyroid development, *Hes1* was detected from E9.5 onwards in the median anlage, and at E11.5 in the ultimobranchial bodies. *Hes1*^{-/-} mouse embryos had a significantly lower number of Nkx2-1-positive progenitor cells (p,0.05) at E9.5 and at E11.5. Moreover, *Hes12/2* mouse embryos showed a significantly smaller total thyroid surface area (-40 to -60%) compared to wild type mice at all study time

points (E9.52–E16.5). In both *Hes1*^{-/-} and wild type mouse embryos, most Nkx2-1-positive thyroid cells expressed the cell cycle inhibitor p57 at E9.5 in correlation with low proliferation index. In *Hes1*^{-/-} mouse embryos, fusion of the median anlage with the ultimobranchial bodies was delayed by 3 days (E16.5 vs. E13.5 in wild type mice). After fusion of thyroid anlagen, hypoplastic *Hes1*^{-/-} thyroids revealed a significantly decreased labeling area for T4 (-78%) and calcitonin (-65%) normalized to Nkx2-1 positive cells. Decreased T4-synthesis might be due to reduced *Nis* labelling area (-69%). These findings suggest a dual role of *Hes1* during thyroid development: first, control of the number of both thyrocyte and C-cell progenitors, via a p57-independent mechanism; second, adequate differentiation and endocrine function of thyrocytes and C-cells.

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* Contributed equally to this work

Plos One

PLOS one

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Genetic Analysis Reveals an Unexpected Role of BMP7 in Initiation of Ureteric Bud Outgrowth in Mouse Embryos

Alexandre Gonçalves, Rolf Zeller

Abstract:

Background: Genetic analysis in the mouse revealed that GREMLIN1 (GREM1)-mediated antagonism of BMP4 is essential for ureteric epithelial branching as the disruption of ureteric bud outgrowth and renal agenesis in *Grem1*-deficient embryos is restored by additional inactivation of one *Bmp4* allele. Another BMP ligand, BMP7, was shown to control the proliferative expansion of nephrogenic progenitors and its requirement for nephrogenesis can be genetically substituted by *Bmp4*. Therefore, we investigated whether BMP7 in turn also participates in inhibiting ureteric bud outgrowth during the initiation of metanephric kidney development.

Methodology/Principal Findings: Genetic inactivation of one *Bmp7* allele in *Grem1*-deficient mouse embryos does not alleviate the bilateral renal agenesis, while complete inactivation of *Bmp7* restores ureteric bud outgrowth and branching. In mouse embryos lacking both *Grem1* and *Bmp7*, GDNF/WNT11 feedback signaling and the expression of the *Etv4* target gene, which regulates formation of the invading ureteric bud tip, are restored. In contrast to the restoration of ureteric bud outgrowth and branching, nephrogenesis remains aberrant as revealed by the premature

loss of *Six2* expressing nephrogenic progenitor cells. Therefore, very few nephrons develop in kidneys lacking both *Grem1* and *Bmp7* and the resulting dysplastic phenotype is indistinguishable from the one of *Bmp7*-deficient mouse embryos.

Conclusions/Significance: Our study reveals an unexpected inhibitory role of BMP7 during the onset of ureteric bud outgrowth. As BMP4, BMP7 and GREM1 are expressed in distinct mesenchymal and epithelial domains, the localized antagonistic interactions of GREM1 with BMPs could restrict and guide ureteric bud outgrowth and branching. The robustness and likely significant redundancy of the underlying signaling system is evidenced by the fact that global reduction of *Bmp4* or inactivation of *Bmp7* are both able to restore ureteric bud outgrowth and epithelial branching in *Grem1*-deficient mouse embryos.

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Reevaluating and Optimizing Polyomavirus BK and JC Real-Time PCR Assays To Detect Rare Sequence Polymorphisms

A. Dumoulin¹ and H. H. Hirsch^{1,2}

Abstract:

PCR-based molecular assays have a central role in polyomavirus diagnostics. To assure optimal performance, target sequences should be regularly updated according to newly available sequences. The aim of this study was to review our in-house polyomavirus BK (BKV) and JC (JCV) real-time PCR assays. Database analysis revealed variations in the BKV target region which might affect the assay performance, while no significant changes were found in the JCV target region. We compared two degenerate versions of our BKV primers which accommodated at least 95% of all pub-

lished genetic variants. Dilutions of cloned viral genomic DNA and probit analysis indicated an analytical sensitivity of the updated BKV assay of 4.15 copies/reaction and that of the JCV assay was 3.37 copies/reaction. The specificity was assessed by testing JCV- and BKV-positive samples that showed no cross-reactivity. The performance of the original and updated BKV assay was compared in 101 urine and 200 plasma samples submitted to our routine diagnostic laboratory revealed similar quantitative results. We conclude that our JCV and updated BKV real-time PCR assays are robust and detect rare variants possibly encountered in the clinical routine.

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Distribution of the auxiliary GABA_B receptor subunits KCTD8, 12, 12b, and 16 in the mouse brain

Michaela Metz¹, Martin Gassmann¹, Bernd Fakler^{2,3}, Nicole Schaeren-Wiemers⁴, Bernhard Bettler¹

Abstract:

GABA_B receptors are the G-protein-coupled receptors for γ -aminobutyric acid (GABA). KCTD8, 12, 12b, and 16 were recently identified as auxiliary GABA_B receptor subunits and distinctly influence biophysical and pharmacological properties of the receptor response. Here we examined the expression patterns of the KCTDs in the mouse brain. Using in situ hybridization analysis, we found that most neurons express KCTD transcripts, supporting biochemical data showing that most GABA_B receptors in the brain incorporate KCTD proteins. In the adult brain, KCTD12 and 16 have a widespread and KCTD8 and 12b a restricted expression pattern. Individual neurons can coexpress multiple KCTDs, as shown for granule cells and CA1/CA3 pyramidal cells in the hippocampus that coexpress KCTD12 and 16. In contrast, granule, Purkinje, and Golgi cells in the cerebellum

selectively express one KCTD at a time. The expression levels of individual KCTD transcripts vary during postnatal brain development. Immunohistochemistry reveals that individual KCTD proteins can exhibit distinct axonal or dendritic localizations in neuronal populations. KCTDs are also detectable in nonneuronal tissues not expected to express GABA_B receptors, suggesting that the role of KCTD proteins extends beyond GABA_B receptors. In summary, our findings support that most brain GABA_B receptors associate with KCTD proteins, but that the repertoire and abundance of KCTDs varies during development, among brain areas, neuronal populations, and at subcellular sites. We propose that the distinct spatial and temporal KCTD distribution patterns underlie functional differences in native GABA_B responses.

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Replicative phenotyping adds value to genotypic resistance testing in heavily pre-treated HIV-infected individuals -the Swiss HIV Cohort Study

Jan Fehr¹, Tracy R Glass², Séverine Louvel^{3,4}, François Hamy³, Hans H Hirsch^{1,4}, Viktor von Wyl⁵, Jürg Böni⁶, Sabine Yerly⁷, Philippe Bürgisser⁸, Matthias Cavassini⁹, Christoph A Fux¹⁰, Bernard Hirschel¹¹, Pietro Vernazza¹², Gladys Martinetti¹³, Enos Bernasconi¹⁴, Huldrych F Günthard⁵, Manuel Battegay¹, Heiner C Bucher², Thomas Klimkait⁴, the Swiss HIV Cohort Study

Abstract:

Background: Replicative phenotypic HIV resistance testing (rPRT) uses recombinant infectious virus to measure viral replication in the presence of antiretroviral drugs. Due to its high sensitivity of detection of viral minorities and its dissecting power for complex viral resistance patterns and mixed virus populations rPRT might help to improve HIV resistance diagnostics, particularly for patients with multiple drug failures. The aim was to investigate whether the addition of rPRT to genotypic resistance testing (GRT) compared to GRT alone is beneficial for obtaining a virological response in heavily pre-treated HIV-infected patients.

Methods: Patients with resistance tests between 2002 and 2006 were followed within the Swiss HIV Cohort Study (SHCS). We assessed patients' virological success after their antiretroviral therapy was switched following resistance testing. Multilevel logistic regression models with SHCS centre as a random effect were used to investigate the association between the type of resistance test and virological response (HIV-1 RNA <50 copies/mL or ≥ 1.5 log reduction).

Results: Of 1158 individuals with resistance tests 221 with GRT+rPRT and 937 with GRT were eligible for analysis. Overall virological response rates

were 85.1% for GRT+rPRT and 81.4% for GRT. In the subgroup of patients with >2 previous failures, the odds ratio (OR) for virological response of GRT+rPRT compared to GRT was 1.45 (95% CI 1.00-2.09). Multivariate analyses indicate a significant improvement with GRT+rPRT compared to GRT alone (OR 1.68, 95% CI 1.31-2.15).

Conclusions: In heavily pre-treated patients rPRT-based resistance information adds benefit, contributing to a higher rate of treatment success.

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REVIEWS

Neutral not a loss: phosphoinositides beyond the head group

Matthias P Wymann¹, Markus R Wenk²

Abstract:

Detection of cellular PtdIns(3,4,5)P₃ by combination of chemical derivatization and tandem mass spectroscopy has been demonstrated.

Phosphoinositide lipids have garnered increased interest in the last two decades because of their importance in physiology and disease. Phosphoinositides consist of an inositol ring head group, which is linked at position 1 via a phosphodiester to a diacylglycerol portion. The inositol head group is dynamically phosphorylated at positions 3, 4 and/or 5 by phosphoinositide kinases. Traditional detection methods are tedious, involve metabolic labeling and only provide information on the phosphoinositide head group but not on the saturated and unsaturated fatty acids in the diacylglycerol part. In this issue Clark *et al.* combine two approaches to improve detection efficiency and sensitivity.

The field of phosphoinositide signaling gained momentum when scientists realized in the early 1980s that phosphatidylinositol(4,5)bisphosphate (PtdIns(4,5)P₂) could be cleaved by phospholipase C to generate inositol (1,4,5) trisphosphate, triggering release of Ca²⁺ from intracellular stores, and diacylglycerol, activating protein kinase C. PtdIns(3,4,5)P₃ was

then discovered in 1988 (ref. 2) and established as the product of class I phosphoinositide-3-kinase (PI3K) and as a key signaling lipid in many biological and disease processes.

In most studies PI3K activity has been monitored indirectly using antibodies to the phosphorylated form of its downstream effector protein kinase B (Akt, also known as PKB). Two findings increased the danger that phosphorylated PKB is not a specific readout for class I PI3K: (i) commonly used PI3K inhibitors target all PI3K family members including PI3K-related kinases, and (ii) one of these, namely mTOR kinase, also phosphorylates Akt/PKB on one of the same residues. In spite of this, the simplicity of immunological detection made it very popular.

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Das Foto entstand im März 2011 in den Dünen des Erg Chebbis, Marokko. Foto: Denise Bielmann

FOTO-ART

Auf dieser Seite möchten wir die schönsten Fotos von Mitarbeitenden veröffentlichen. Alle Fotos, die an die Redaktionsadresse dbmfacts@unibas.ch gesandt werden, nehmen an der Wahl teil.

On this page we will present the best photos taken by staff. All photos submitted by email to the editorial office address dbmfacts@unibas.ch will be considered.

**DEPARTEMENT
BIOMEDIZIN
USB**



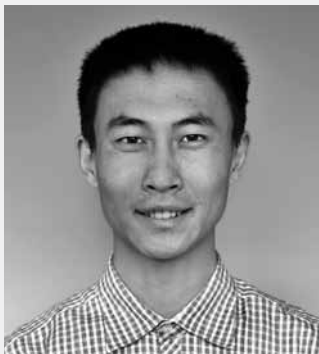
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Ocular Pharmacology and
Physiology



Yvonne Fink
Cancer Immunology



Axel Karow
Exp. Hematology



Weijie Chen
Gyn. Oncology



**Carolina Maria Medeiros
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Lisa Adelfinger
Synaptic Plasticity



Dieter D'Hoedt
Cellular Neurophysiology

Ausserdem haben angefangen:

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Marijn Anneveld, Cardiobiology

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Petra Pfenninger, Developmental and Molecular Immunology

Panagiotis Tsapogas, Developmental and Molecular Immunology

INSTITUT FÜR MEDIZINISCHE MIKRO- BIOLOGIE

Gunhild Unterstab, Transplantation Virology

Ilija Lujic neuer IT-Supporter



Am 23. Mai 2011 hat Ilija Lujic seine Tätigkeit als IT-Supporter am Departement Biomedizin USB begonnen. Mit dem USB vertraut war er zu diesem Zeitpunkt schon. Reto Schaub hatte dringend Support für die Abteilung Prozessunterstützung und Informatik am USB benötigt, der er ja bekannterweise vorsteht, und war dabei auf Ilija gestossen. Da das Projekt gestoppt wurde, für das er angestellt worden war, war Ilija just auf der Suche nach einer neuen Stelle, als das DBM die Position von Ismerai Steiner ausschrieb. Und so kam es, dass unter den vielen Bewerbungen, die eingingen, auch Ilijas war. Ilijas Informatikerlaufbahn begann bei den Zentralen Informatik-Diensten der Kantonalen Verwaltung Baselland, bei denen er seine Ausbildung absolvierte. Anschliessend hängte er seinen Militärdienst als Durchdiener an, das heisst als Milizsoldat, der seinen gesamten Militärdienst in 300 Tagen erfüllt. Erste Erfahrungen als In-

formatiker sammelte Ilija bei Clariant und am USB, bevor er zu uns stiess. Ilijas Familie kommt ursprünglich aus Serbien, heute lebt der eine Teil der Familie in Bosnien, der andere in der Schweiz. Das Serbokroatische hat Ilija zur Freude seiner Eltern noch nicht verlernt. Seine Freizeit verbringt Ilija gerne im Familien- und Freundeskreis, beim Sport sowie, wenn Zeit übrig bleibt, beim Gitarre spielen - und wenn wundert's am Computer.

Ilija, wir heissen Dich herzlich willkommen und wünschen Dir viel Freude und Erfolg bei Deiner neuen Tätigkeit!

Heidi Hoyermann

Congratulations

Das DBM gratuliert ganz herzlich!



Anni Göritz-Pelttari

Geboren am 01.06.2011



**Mélisandre
Schlicklin-Traunecker**

Geboren am 02.05.2011



Sophie Ruby Khan-Seidel

Geboren am 09.05.2011



**Julian Neel
Gremmelmaier-Khanna**

Geboren am 06.04.2011

***Herzlich
willkommen,
allerseits!***



Elea Charlotte O'Meara-Stern

Geboren am 07.03.2011



Mathias Vavassori

Geboren am 10.05.2011

Zur Emeritierung von Uwe Otten

Aus Anlass der Emeritierung von Uwe Otten, Professor für Physiologie, hat am 28. April 2011 im Anatomischen Institut ein attraktives und gut besuchtes wissenschaftliches Symposium stattgefunden. Seit fast 40 Jahren hat Uwe an der Universität Basel geforscht und gelehrt. Uwe studierte Medizin in Lübeck und ist nach seiner medizinischen Weiterbildung in Hannover (Chirurgie und Innere Medizin) 1972 zur Arbeitsgruppe von Hans Thoenen in der Abteilung Pharmakologie des Biozentrums gestossen, wo er bis 1978 an der Regulation von Tyrosin Hydroxylase und von Nerven Wachstums-Faktor (NGF) gearbeitet hat. Von 1979 bis 1989 leitete er seine eigene Arbeitsgruppe am Biozentrum. Während dieser Zeit sind wichtige Arbeiten zur Interaktion zwischen Nervensystem und endokrinem System einerseits sowie zwischen Nerven- und Immunsystem andererseits entstanden. Diese wegweisenden Arbeiten sind ihrer Bedeutung entsprechend in Nature, PNAS und Science publiziert worden. 1989 wurde Uwe Otten zum Professor am Physiologischen Institut berufen. Sein Interesse galt dort vor allem den Interaktionen zwischen Nerven- und Immunsystem, speziell den Neurotrophinen und Zytokinen in Zusammenhang mit Neuroregeneration, sowie neurodegenerativen und inflammatorischen

Krankheiten. Neben seiner wissenschaftlichen Arbeit war Uwe Otten besonders engagiert in der Lehre und war bei den Medizin-Studenten für seine fundierten Vorlesungen äusserst beliebt.

Am Abschiedssymposium haben mehrere von Uwe Otten's früheren und jetzigen wissenschaftlichen Weggefährten über ihre neueren Arbeiten berichtet. Die Professoren Michael Frotscher und Klaus Unsicker (Universität Freiburg i.Br.), Michael Goedert (MRC, Cambridge) und Stefan Rose-John (Universität Kiel) präsentierten nicht nur ihre aktuellen Forschungsergebnisse, sondern nahmen auch ausgiebig Bezug auf ihre wissenschaftlichen und privaten Kontakte zu Uwe Otten. Am Schluss des Symposiums reflektierte Uwe Otten über seine Zeit an der Universität Basel, bevor sich Freunde und Kollegen in festlicher Runde zum leiblichen Teil des Symposiums trafen.

Besonders am Herzen lagen Uwe Otten in den letzten Jahren die Kontakte zu den Medizin-Studenten. Auch nach seinem offiziellen Abschied wird er die Studenten nicht vollständig vermissen müssen, hat er doch zugesagt, uns Physiologen gelegentlich weiterhin in der

Lehre unterstützen. Dafür sowie für die jahrelange kollegiale Zusammenarbeit danken wir ihm herzlich. Wir wünschen ihm und seiner Frau alles Gute für den kommenden Lebensabschnitt und weiterhin viel Freude beim Verfassen von Artikeln zu neuroinflammatorischen Themen.

Bernhard Bettler
Josef Bischofberger
Hansruedi Brenner
Marijke Brink



“Sister, sister, come and look”

Ein Arbeitstag in der Shanti-Station in Kathmandu/Nepal

Um 05.00 Uhr morgens werde ich vom lauten Gebetsgesang des durch die Strassen eilenden Muezin jäh aus dem Schlaf gerissen. Vom Bett aus erlebe ich dann allmorgendlich einen atemberaubenden Sonnenaufgang im dichten Dunst. Die zweithöchste Smogkonzentration weltweit macht dieses Naturschauspiel möglich.

Nach einem lauwarmen Instantkaffee und einem improvisierten Müesli erledige ich meinen campinghaften Haushalt. Eine Küche gibt es in meiner Unterbringung, die sich Hotel nennt, nicht. Das Haus liegt in Gaushala, einem bescheidenen Wohnviertel in der Nähe eines Slums und der Shanti-Klinik, dem Lepra- und Behindertenzentrum, in dem ich für knapp sechs Wochen als Volunteer arbeite.

Um 8.30 mache ich mich auf zur Arbeit. Vorbei an Abfallhalden, Koch- und Fruchtständen gelange ich auf die Ringroad, eine sechsspurige Strasse, die gleich einem Gürtel rund um Kathmandu führt. Das kurze Stück auf dieser Strasse erfordert jeweils höchste Aufmerksamkeit. Der «Gehweg» dient Bussen, Autos und Hunderten von Motorrädern als Überholspur.

Mein Weg führt mich vorbei am Pashupathinath-Tempel, in dessen Nähe immer einige Leichen auf den Aryu und Surya Ghats am Verbrennen sind. Aryu steht für die Verbrennungsstätten der höheren, Surya für die niederen Kasten. 300 kg Holz muss man pro Leiche rechnen. Das geht alles in

die Luft und die Asche in den Bagmati-Fluss – an jener Stelle eine Kloake. Weiter, vorbei an einigen armseligen Bretterbuden, komme ich in eine slumähnliche Gegend, in der die Shanti Sewa Gria Klinik liegt.

Ich werde von den Bewohnern der Klinik freudig begrüsst, verneige mich, mit vor der Stirn gefalteten Händen und Namasté murmelnd, nach links und nach rechts. Ich gebe mir dabei grosse Mühe, niemanden zu übergehen. Sawitri, eine Nepali, steht schon bereit, um alle Mitarbeitenden zu segnen, so komme auch ich zu einem Bindi, einem roten Punkt auf der Stirn. Weiter geht's in die Klinik, eher in ein Wohnheim, hinüber, wo die Patienten bereits in langen Schlangen geduldig sitzen und auf einen Arzttermin warten.



Ein Leichnam ist fast verbrannt.



Manosh und Frances.

“Sister, sister, come and look” hallen mir die Rufe von Manosh, einem Jungen von cirka 18 Jahren entgegen. Er will der Erste sein und mir voller Stolz zeigen, wie weit er mit Stricken, das ich ihm beigebracht habe, bereits gekommen ist. Es berührt mich sehr zu sehen, wie er mit seinen schwerstverkrüppelten Fingern, vermutlich eine seltene Erbkrankheit, niemand weiss es so genau, sich abmüht und dabei wunderschön strickt. Es soll ein Überziehpulli für Ruth Gonseth werden, die Schweizer Ärztin, durch die ich Shanti kennen lernte und die auch dort arbeitet. Gott sei Dank gibt es email, sofern man Strom hat, so kann ich meine Schwester um eine Pulli-anleitung bitten, denn von Stricken habe ich nur marginal eine Ahnung.

Die jungen Frauen im 2. Stock der Klinik, alle an den Rollstuhl gefesselt, auf Grund von Rücken-TB, Polio oder Unfällen, wollen bald alle ebenfalls stricken. Also organisiere ich verschiedenfarbene Wolle, um mit ihnen Mützen, Amedysli und Schals anzufertigen, die man

den Schulkindern abgeben oder aber an einem Bazar verkaufen kann, was wiederum etwas Geld in die Kassen spült. Im Rollstuhlzimmer herrscht fröhliches Lachen und emsiges Treiben. Die Frauen sind glücklich, etwas arbeiten zu können, was Balsam für ihr Selbstwertgefühl ist. Ambica, eine geistig stark zurückgebliebene junge Frau, fuchtelte mit einem Heft vor mir herum, bis ich verstehe, dass sie zur Schule gehen möchte. Ich setze mich zu ihr und versuche ihr beizubringen, ihren Namen ab Vorlage zu schreiben. Sie ist stolz und besteht fortan auf ihren Unterricht.

Weiter geht es zu einem ein cirka 50 jährigen Mann, seine Beine sind amputiert, er sitzt im Rollstuhl. Tag für Tag sitzt er da und starrt vor sich hin. Mir fällt sein trauriger Blick auf, der mir immerzu folgt. Ich erfahre aus einem fragmentarischen Gespräch, er auf Nepali, ich auf Englisch..., dass auch er etwas arbeiten möchte. Also gehe ich in die Werkstatt, wo viele Leprakranke damit beschäftigt sind, trotz ihren Verstümmelungen wahre

Kunstwerke zu vollbringen, sei es Puppen nähen, Karten malen, Geschenkpapier bedrucken. Ich bringe ihm Karten und er beginnt, Vögel mittels Schablonen auf Karten zu stanzen, die dann von einem weiteren Mitarbeiter ausgemalt werden.

Weiter geht es ins Verbandszimmer, wo ich Sharita und Jaja, zwei Nepalifrauen, die in Wundpflege ausgebildet wurden, helfen soll, ein Patientenblatt auf Englisch auszufüllen. Sie bitten mich immer wieder, die Wunden anzuschauen und zu beschreiben (nicht gerade appetitlich), bis ich realisiere, dass sie sich, aus Angst vor Fehlern, nicht getrauen, Englisch zu schreiben. Also beginne ich, die zwei täglich in Englisch zu unterrichten, anfangs mittels eines Dolmetschers. Sie lernen schnell und am Ende meines Aufenthalts füllen sie die Patientenblätter alleine und selbstsicher aus.

Dann gehe ich zu den zwei schwerstbehinderten Mädchen: Sunita, cirka vier Jahre alt, liegt in einer Holzki-

ste, kann aber mit Hilfe und gestützt von Kissen sitzen. Vermutlich kann sie auf einem Ohr hören, denn nach einigen Wochen reagiert sie, wenn ich sie beim Namen rufe. Das sind dann so die kleinen grossen Glücksmomente... Dann ist da noch Asa, cirka acht Jahre alt. Sie ist nicht nur blind, sondern auch taubstumm. Somit läuft eine gewisse Kommunikation nur über Körperkontakt. Es ist schwer auszuhalten, dieses Kind immer auf dem nackten Boden liegen zu sehen. Hinzukommt, dass die zwei Mädchen ziemlich verwahrlost sind, da ihre Betreuungsfrauen, zwei ehemals Lepra-Kranke nicht sehr liebevoll mit ihnen umgehen. Ergo, schreibe ich mir auf die Fahne, ihre Betreuerinnen, die sich so einige Rupien verdienen, etwas zu schulen. Dies gestaltet sich als äusserst schwierig. Im Hinduismus spricht eine Behinderung für schlechtes Karma und diese Menschen gehören somit zum Abschaum. Ich versuche den zwei Nepali etwas anderes vorzuleben, was bei der einen Frau auf Interesse stösst, bei der anderen aber nur Groll gegen mich herauf beschwört.



Ein Behandlungszimmer der Klinik.



Alltag im Slum.

Um 13.00 treffen wir Volunteers und die Ärzte sich zum gemeinsamen Essen in einer winzigen Küche, das Highlight des Tages. Am Nachmittag gehe ich dann wieder ins Spital, wo ich mich um einen Stroke-Patienten kümmere, in dem ich seine verkrampfte Hand massiere und ihm etwas Zuwendung schenke. Verstehen kann ihn niemand. Oder ich führe das blinde Grossmütterchen in den Hof zu einem Spaziergang. Dabei redet die alte Frau unentwegt auf mich ein. Alles, was ich verstehe, ist, dass sie immer nach Schokolade fragt.

Am Abend, zurück im Hotel, bin ich dann jeweils todmüde und glücklich, wenn ich Wasser zum Duschen und zum Waschen meiner Kleider habe. Um 18.30 ist es dann bereits stockfinster und meist wird dann auch

noch der Strom, da es davon zu wenig gibt, abgestellt. Dann hänge ich im Schein einer Kerze meinen Gedanken nach oder lese mit einer Taschenlampe.

Die Idee, so einen Einsatz zu leisten, kam mir vor fünf Jahren auf einer Reise durch Burma, wo grösste Armut und politische Grausamkeit an der Tagesordnung sind. Ich bereue keinen einzigen Augenblick, diesen Schritt getan zu haben. Erhält man doch einen tiefen Einblick in eine andere Kultur und wird immer wieder von der grossen Dankbarkeit und der bescheidenen Zufriedenheit dieser in unermesslicher Armut lebenden Menschen reich beschenkt. Es relativiert so manches.

Frances Kern

Sportschütze Yves Hartmann führt uns in die Welt des Schiesssports ein:

Wo «Hobby-Rambos» fehl am Platz sind

Sportliches 300m-Schiessen mit Armeewaffen

Schiessen als Sport

Schiessen als Vereins- und Leistungssport zählt zu den populärsten Freizeitaktivitäten. Praktisch jedes Dorf zwischen Nordsee und den Alpen verfügt über einen Schützenverein. Dort wird das Schiessen regelmässig und mit Enthusiasmus als Sport gepflegt.

Sportschiessen hat eine lange Tradition

Sportschiessen entwickelte sich aus der Jagd mit Wurfgeschossen, dem mittelalterlichen Bogen- und Armbrustschiessen und schliesslich dem Einsatz neuzeitlicher, hochpräziser Schiesssportgeräte. Nach der schnellen Verbreitung des Schiesswesens werden seit 1890 Weltmeisterschaften veranstaltet, seit 1896 zählt Schiessen zum olympischen Programm.



A-Scheibe und Zielbild



B-Scheibe und Zielbild

Der pädagogische Wert des Schiessportes

Untersuchungen bei verschiedenen Sportarten ergaben, dass Sportschützen sich besser und länger konzentrieren können. Die Konzentrationsfähigkeit und Ausdauer, aber auch die Fähigkeit, Informationen «blitz-schnell» aufzunehmen, zu verarbeiten und in feinmotorische Handlungen zu übertragen, charakterisieren das Sportschiessen als zeitgemässe Sportart des modernen Menschen.



Stgw 90

Was ist Sportschiessen?

Sportschiessen ist eine anspruchsvolle Tätigkeit, die gute Nerven, eine gute Grundkondition und eine gesunde Portion Ehrgeiz verlangt. Kurzum ein Sport, der viel Freude bereitet und vom Jungschützen bis zum Veteranen gleichermassen zu begeistern weiss. In kaum einer anderen Sportart kann z. B. ein 16jähriger Jungschütze zusammen mit seiner Schwester, dem Vater – und wenn er noch rüstig ist – dem Grossvater in der gleichen Mannschaft resp. Gruppe um die Wette konkurrieren.

Was ist Sportschiessen nicht?

Sportschiessen ist kein Zusammentreffen von «Hobby-Rambos» oder eine verkappte Bürgerwehr.

Wie geschossen wird

Es wird im Liegen geschossen.

Wichtig dabei sind die richtige Stellung (ja genau: sich richtig bequem und stabil hinlegen), den sogenannten äusseren Anschlag, und auch «innere» Faktoren wie Atemtechnik, Schussabgabe, Konzentration, Entspannung und richtiges Zielen. Gezielt wird wie aufgezeigt.



Stgw 57

Unser Verein

Wo schießt unser Verein?

Wir schießen im Schiessstand Mühlerain in Allschwil, in der Nähe der Schule für Blindenführhunde. Für den Schiessbetrieb werden öffentliche Wege mit Verbots- und Warnschildern abgesperrt.

Angaben zu meiner Waffe: Sturmgewehr 90

Gesamtlänge	1000 mm
Kaliber	5,6 mm
Lauflänge	528 mm
Visier	Dioptr-Visier mit Irisblende
Länge der Linie Visier – Korn	540 mm
Technische Kadenz	600–900 Schuss/Min
Gewicht der Waffe mit vollem Magazin	4350 g
Mündungsgeschwindigkeit (Vo)	905 m/s
Gasdruck	max 4200 bar

Um die Lärmemissionen des Schusses herab zu setzen, schiessen wir durch Lärm schluckende Tunnels. Der Knall, welcher durch den Eintritt der Kugel in den Überschall entsteht, kann jedoch nicht abgeschwächt werden.

Was macht unser Verein?

In unserem Verein wird ausnahmslos mit Ordonanzwaffen geschossen.



Karabiner 11

Ausser, dass wir uns in vereinsinternen Wettkämpfen, wie auch mit anderen Vereinen, messen, haben wir von der Eidgenossenschaft den Auftrag, den aktiven Wehrmännern zu ermöglichen, ihrer Schiesspflicht nach zu kommen.

Dafür organisieren wir an speziellen, öffentlich publizierten, Tagen die sogenannten obligatorischen Übungen.

Wir betreuen die Schützen und gewährleisten einen unfallfreien Schiessbetrieb.

Auch organisieren wir jedes Jahr einen Jungschützenkurs. Dieser bereitet Jugendliche ab 16 Jahren auf die Handhabung der Waffe vor und gilt als vordienstlicher Kurs, vor dem eigentlichen Militärdienst. Der Verein ist konfessionell und politisch neutral.



Karabiner 31

Einmal im Jahr machen die aktiven Schützen unseres Vereins einen zwei- bis dreitägigen Ausflug an ein Schützenfest (meist an Kantonale und alle 5 Jahre ans Eidgenössische).

Wie ich zu dieser Sportart kam

Von den Schützenvereinen werden in der Schweiz jedes Jahr sogenannte Jungschützenkurse durchgeführt.

Da mein älterer Bruder diesen Kurs vor mir besuchte, war dies für mich irgendwie fast Pflicht.

Ich fand Gefallen an dieser Mischung aus Konzentration, Präzision und Kameradschaft.

Als ich meine zivile Ausbildung abgeschlossen hatte und als aktives Mitglied eintrat, durfte ich auch gleich in den Vorstand des Vereins und mit Abschluss meiner militärischen Ausbildung wurde ich mit 23 Jahren zum Präsidenten gewählt, was ich nun seit 17 Jahren auch geblieben bin. Seit 1991 habe ich auch die Ausbildung und Funktion zum Schützenmeister. Diese Ausbildung beinhaltet die Betreuung von Schützen, das Wissen über die gestatteten technischen Hilfsmittel, die Sicherheitsvorschriften in und um den Schiessstand und die administrativen Pflichten gegenüber dem Staat.

Meine persönliche Meinung zu «speziellen» Schiessstätigkeiten

Im Gegensatz zum Sportschiessen, bei dem auf abstrakte Scheiben geschossen wird (sei es mit Gewehr oder Pistole), finde ich das sogenannte Gotcha- oder Paintball-Schiessen gefährlich, da hier bewusst durch die Gewöhnung, auf andere Menschen zu zielen und ab zu drücken, die Hemmschwelle herabgesetzt wird.

Die Scheiben aus Sicht vom Schiessstand (links). Das Lager von Seite der Scheiben (rechts).



Die Scheiben aus Sicht vom Schiessstand (links). Das Lager von Seite der Scheiben (rechts).

Gheymeh Bademjan (Split-Pea and Eggplant Stew)

Ingredients (for 4 people):

- lamb or beef 500g
- Split-peas, 170g
- Eggplant 250g
- Onions 1
- Potatoes 200g
- Oil
- tomato paste
- 3–4 crushed, dried limes (small ones with sour taste); freshly-squeezed lime juice can be used instead
- Salt
- Black pepper
- Spices (turmeric, cinnamon)

Peel the onion and chop it in small pieces after that put 2 tablespoons of oil in a deep pot and fry the onion with the meat until the onion is lightly colored then add pepper, turmeric and tomato paste follow by adding water. Let it simmer until meat is medium cooked then add the split-peas until the meat is tender and the split-peas are well cooked.



Meanwhile, peel the eggplant and cut it lengthwise in half. (Cut it in half again if you are using a large eggplant). Fry the eggplant in oil until it is lightly colored. Remove and keep to the side.

Then peel and chop potatoes like French fries. Fry them until getting golden color and keep them a side.

When the meat is tender, place the eggplant on top of the stew and add dried limes/ freshly-squeezed lime juice, salt and cinnamon to taste. Add more water if its required (if the dish doesn't look

liquidly then it will need more water). Let the mixture boil for another few minutes. Taste and adjust the seasoning. When it is ready to serve add the potatoes on top of the stew.

Serve this dish hot with rice.



Zeinab Berekati

Vivian Kiefer-Vargas, Gyn. Oncology

"God gave me nothing I wanted, but he gave me everything I needed" ...

... this has been my motto all my life, and today blessed with three children, two grandchildren, a long-standing marriage and career, I feel that indeed I have everything I ever needed.

Born in Manila, Philippines to a large family, I learned at a very early age to appreciate all that came my way, especially the sacrifices my parents made in order to give us a decent education as this was the key to having any future at all. In 1972, equipped with a Bachelor's degree, I abandoned all that was familiar and settled my roots in

Switzerland taking up a position as a Medical Technologist in the Chemistry laboratory of Kantonsspital Liestal where I worked until 1988 in between marrying and starting my family.

From 1988 to 1990 I joined Hoffman La Roche AG, Switzerland as a Microbiology Research Tech-



(From left to right) "Cook" and colleague Corina, Vivians daughter Sharon, Vivian with grandchild Jada and "kitchen help" and colleague Zeinab at a Paella Party in summer 2010.

nician, followed by six years as a Biology Research Technician. In 1997 I joined the University Women's Hospital, Basel as a Research Technician in the Laboratory for Prenatal Medicine where I still work today.

I have contributed significantly to furthering research in the above laboratories, with my main focus being towards extraction of plasma and serum from blood, isolation of DNA and RNA from plasma and serum, immunohistochemistry, fluorescence in-situ hybridization (FISH), enrichment of rare fetal hemopoietic cells from the circulation of pregnant women using the magnetic cell sorting method (patented by the Laboratory for Prenatal Medicine). I also regularly train many research students and foreign students of at least 8 different nationalities.

Despite my many successes, the plight of the Filipinos, especially the migrant workers, was always close to my heart. Wanting to give something back to my home country, in 1995 I joined Maharlika-Switzerland, a Filipino organization with a two-fold purpose, to help Filipino migrants across Switzerland to preserve their Filipino culture as well as to increase Swiss and foreigner's awareness of Filipino customs and traditions through various festivities and events. On the other side I wanted to help the Filipinos through the initially daunting matrix of the Swiss system, by providing them information and imparting knowledge through workshops and talks on the Swiss pension system, health, German language lessons, team-building, and counselling.

The individual projects carried out by Maharlika in the Philippines:

Skills Training in Massage Therapy and Reflexology, Manila
Beneficiaries: Unemployed women especially mothers and out of school youth

Meat Processing and Food Preservation, Manila
Beneficiaries: Unemployed women especially mothers and out of school youth

Feeding Program in the celebration of the nutrition month on July 2010, Manila
Beneficiaries: All the kids enrolled on the Day Care Centres.

Mid June 2011 the Swiss Lottery guaranteed an aid package of 121,000 CHF to benefit the project to build a multipurpose hall in Sitio 3 in Barangay Fort Bonifacio (Taguig City, Philippines); in Sitio 1, Sitio 2, Sitio 3 and Sitio 4 the 12'000 residents (that means 43% of Barangay population) still live below the poverty line.



Vivian and her husband Willy at Phuket.

As the years went by, I ensured Maharlika became increasingly active in organizing and financing development and charity projects in the Philippines. We were able to raise over 5 million Philippine Pesos in support of many projects including funding construction of school buildings across the Philippines, day care centres for special children, multi-purpose halls, concreting roadways and improvement of facilities, setting up feeding programs and we were featured in many Basel based newspapers as well as receiving the Presidential

Award from the Philippine president.

Juggling full-time work in the lab, raising children, and helping Filipinos took over the most part of my life so that there were never enough hours in the day to even begin a hobby.

Now that my son Stefan, daughter Sharon are married with children, and my other daughter Nicole is working full-time as a teacher, I feel I can finally take my first break in 40 years to take up my passions in life for travelling with my husband, recently returning from a pilgrimage to India where I got to pay homage to another passion, my religious beliefs. My time is divided between being a grandmother to my 1 year old grandson and 2.5



Home for the abandoned old people, Montalban, Philippines

year old granddaughter, cooking and tasting international cuisines, spending time gardening while still working hard to help various charity projects in the Philippines

as well as offering counselling and advice here in Switzerland.

Today, I feel I have accomplished all that I could hope for.

What Vivian didn't say:

In addition to the projects mentioned above Vivian was able to personally do the following projects with her husband:

Philippines: gave financial help to home for the aged; distributed rice and canned goods to 800 to 1000 families every two years; helped addicted children (street children), gave financial help to rehabilitation; gave counselling (marriage, financial); assisted Filipinos in finding jobs.

Iran: supported cancer patients and underprivileged families financially

Egypt: supported cancer patients financially

India: gave financial help to mentally retarded children and school children, gave financial help to 1000 to 1500 malnourished people every last Thursday of the month.

In addition to all of the above Vivian was also very successful politically:

From 1995 to 2010 Vivian was the president of the association for Filipino migrants "Maharlika Schweiz", was a member of the Forum for Integration and Migration in the Basel region from 2000 to 2004, was chosen by the Swiss Federal Council to be a member of the The Federal Commission for Foreigners from 2000 to 2007 and is also a member of the Swiss Forum for Integration and Migration.



*3rd DBM Summer
Barbecue*

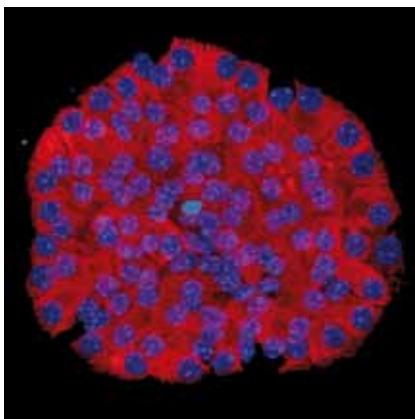
*Wednesday, August 24,
2011*

*at the Langehof in
Schonenbuch*

*walking-tour, barbecue,
several attractions*

VORSCHAU PREVIEW

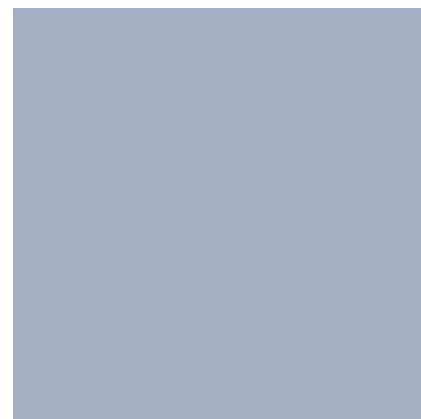
In der nächsten Ausgabe ...



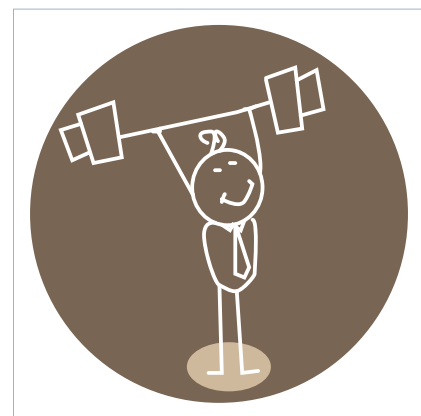
... entführt uns Marc Donath in die Welt der Diabetes-Forschung



... nimmt uns Gennaro De Libero mit in das wissenschaftliche Singapur



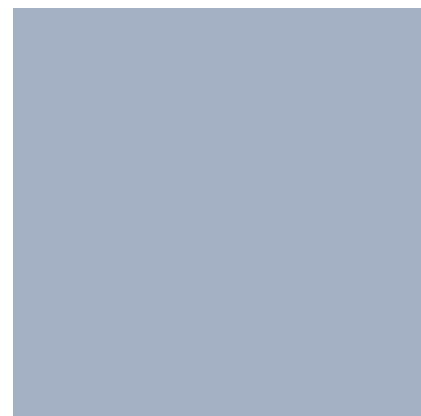
... lernen wir mit Benjamin Pippenger seine Heimat Montana kennen



... bauen wir mit Bilal Azakir Muskeln auf



... freuen wir uns auf die schönen Seiten des Herbstes



Meer

Wenn man ans Meer kommt
soll man zu schweigen beginnen
bei den letzten Grashalmen
soll man den Faden verlieren

und den Salzschaum
und das scharfe Zischen des Windes einatmen
und ausatmen
und wieder einatmen

Wenn man den Sand sägen hört
und das Schlurfen der kleinen Steine
in langen Wellen
soll man aufhören zu sollen
und nichts mehr wollen nur Meer
Nur Meer

Erich Fried

